## Summary Table of Study Protocol

| | |
|---|---|
| **Title** | A Postmarketing Prospective Cohort Study of Melanoma Patients Treated With IMLYGIC® (Talimogene Laherparepvec) in Clinical Practice to Characterize the Risk of Herpetic Infection Among Patients, Close Contacts, and Health Care Providers; and Long-term Safety in Treated Patients |
| **Protocol version identifier** | 20130193, **Superseding** Amendment 5 |
| **Date of protocol version** | Original: 18 April 2016<br>Amendment 1: 28 July 2016<br>Amendment 2: 12 April 2017<br>Amendment 3: 03 September 2020<br>Amendment 4: 26 August 2021<br>Amendment 5: 25 August 2022<br>**Superseding Amendment 5: 12 October 2022** |
| **European Union postauthorization study register number** | EUPAS15128 |
| **Active substance** | Talimogene laherparepvec |
| **Medicinal product** | IMLYGIC® |
| **Product reference** | To be determined |
| **Procedure number** | EMEA/H/C/002771 |
| **Research question and objectives** | The primary objective is to estimate the incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients enrolled in Study 20130193 for up to 5 years after the first IMLYGIC dose |
| **Countries of study** | Inclusion of specific countries will depend on postmarket use of product, local feasibility, and local regulatory requirements. |
| **Author** | PPD<br>Center for Observational Research<br>PPD<br><br>PPD<br>Center for Observational Research<br>PPD |

**Marketing Authorization Holder**

| | |
|---|---|
| **Marketing authorization holder** | Amgen Inc.<br>One Amgen Center Drive<br>Thousand Oaks, CA 91320-1799<br>United States<br>1-805-447-1000 |
| **Marketing authorization holder contact** | PPD |

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

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**Investigator's Agreement**

I have read the attached protocol entitled "A Postmarketing Prospective Cohort Study of Melanoma Patients Treated With IMLYGIC® (Talimogene Laherparepvec) in Clinical Practice to Characterize the Risk of Herpetic Infection Among Patients, Close Contacts, and Health Care Providers; and Long-term Safety in Treated Patients", dated **12 October 2022**, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

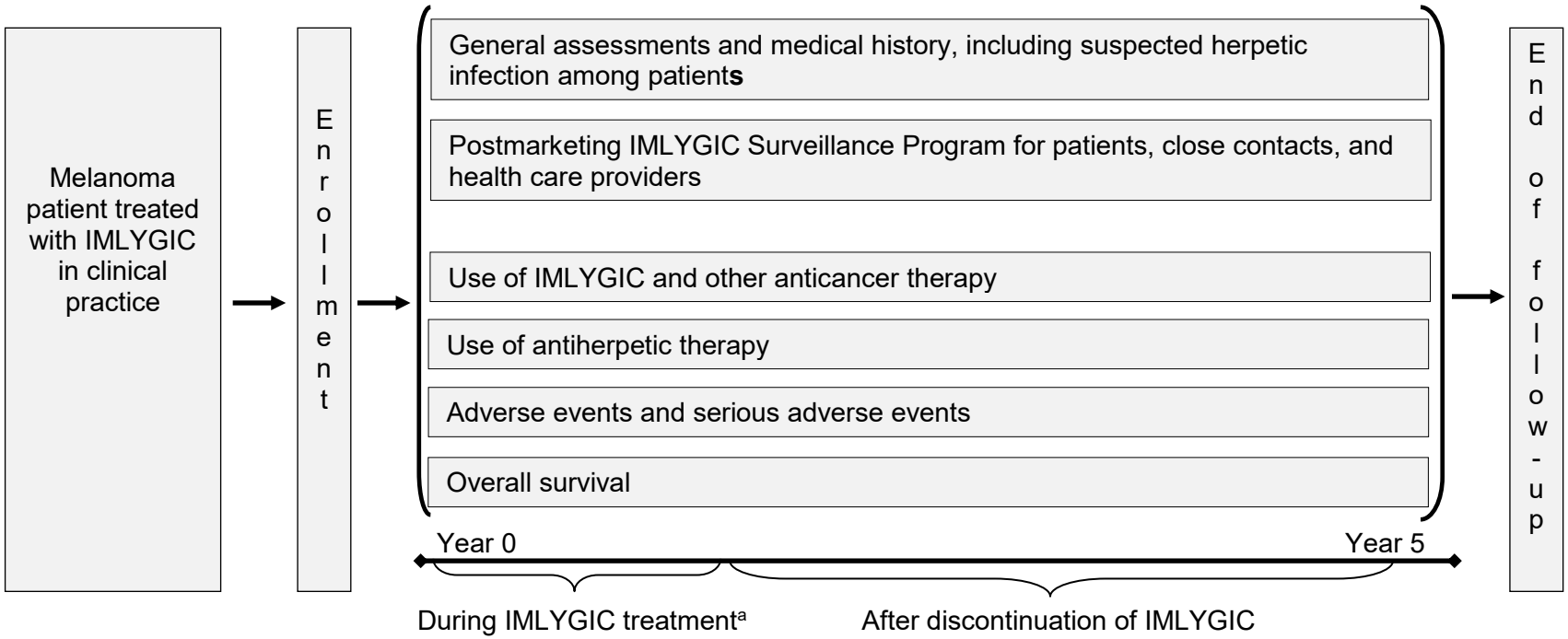
| Signature | |
|---|---|
| Name of Investigator<br>*Title:*<br>*Name of Hospital/Site:*<br>*Address/City/State/Country:*<br><br>*Phone Number:*<br>*Email:* | Date (DD Month YYYY) |

**Study Design Schema**

Follow-up

- observation during and after IMLYGIC® treatment
- during IMLYGIC treatment, study assessments at clinic visits for IMLYGIC treatment
- after discontinuation of IMLYGIC, study assessments every 3 months (± 30 days) via phone or routine clinic visits if they fall within the 30-day window

**Collection of data from the following:**




[a] Median duration of IMLYGIC treatment was approximately 6 months in the clinical trial setting but may differ in clinical practice.

## Table 1. Schedule of Assessments

| | Screening[a] | Baseline | Assessments (approximately every 2 weeks) during IMLYGIC® treatment[b] | Assessments (every 3 months ± 30 days) after discontinuation of IMLYGIC[c] |
|---|---|---|---|---|
| **General assessments and medical history** | | | | |
| Written informed consent | x | | | |
| Review of eligibility criteria | x | | | |
| Patient demographics[d] | | x | | |
| Patient characteristics[e] | | x | | |
| Medical and surgical history[f] | | x | | |
| History of herpetic infection[g] | | x | | |
| Signs and symptoms of herpetic infection[h] | | | x | x |
| Results of local laboratory testing of suspicious herpetic lesions for HSV-1, per standard of care | ← At any time → | | | |
| **Treatment received** | | | | |
| IMLYGIC[i] | | x | x | |
| Other anticancer treatment[j] | | x | x | x |
| Antiherpetic therapy[k] | | x | x | x |
| **Assessments of Safety and Survival** | | | | |
| Review of adverse events and serious adverse events during IMLYGIC treatment[l, m] | | x | x | |
| Review of IMLYGIC-related adverse events and serious adverse events that occur after discontinuation of IMLYGIC[n] | | | | x |
| Review of product complaints[o] | | x | x | |
| Review of other safety findings[p] | | x | x | |
| Survival assessment[q] | | | x | x |



Footnotes are defined on the next page of this table

## Table 1. Schedule of Assessments

| | Screening[a] | Baseline | Assessments (approximately every 2 weeks) during IMLYGIC® treatment[b] | Assessments (every 3 months ± 30 days) after discontinuation of IMLYGIC[c] |
|---|---|---|---|---|
| **Results from analysis of samples for talimogene laherparepvec DNA** | | | | |
| Patient[r] | ← At any time → | | | |
| Close contact[r] | ← At any time → | | | |
| Health care provider[r] | ← At any time → | | | |

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HSV-1 = herpes simplex virus type 1, **HCP = Health care provider, qPCR = quantitative polymerase chain reaction**.

[a] The study site will maintain a screening tally of patients receiving IMLYGIC that includes nonidentifying information about sex, age, **race, ethnicity,** and disease stage.

[b] During IMLYGIC treatment, the study assessments are to be completed at the clinic visits for IMLYGIC treatment.

[c] After discontinuation of IMLYGIC until the end of follow-up, the study assessments are to be completed every 3 months (± 30 days) via phone or routine clinic visits if they fall within the 30-day window.

[d] Review the following patient demographics: age, sex**, race, and ethnicity**.

[e] Review the following patient characteristics: Eastern Cooperative Oncology Group (ECOG) performance status and disease stage.

[f] Review medical and surgical history:

- surgical therapy
- radiotherapy
- local or regional therapy
- systemic therapy
- participation in clinical trials

[g] Patient reports the following information on herpetic infections: type of infection, frequency, and testing; type of treatment.

[h] Patient reports presence or absence of signs and symptoms of suspected herpetic infection since the time of last observation.

- Patient's response ("yes" or "no") to the following question will be recorded: "Have you had any signs or symptoms of herpetic infection since your last visit?"
- Examples of signs and symptoms include **but not limited to**: pain, burning, or tingling in a blister around the mouth or genitals**,** fingers**,** ears**, or any part of the body close to or far from the injection site**; eye pain, light sensitivity, discharge from the eyes, or blurry vision; weakness in arms or legs; extreme drowsiness; mental confusion.
- If a patient answers "yes", then the following information about the infection will be collected: signs and symptoms, dates, reporting and testing for virus identification, and antiherpetic treatment received.

[i] Record the following information about IMLYGIC received: dates, dose concentration, injection volume.

[j] Record dates and types of other anticancer therapy received (see "f" for the list of therapies).

[k] Record the following information about antiherpetic therapy received: dates, type (eg, acyclovir, valacyclovir, famciclovir, docosanol), administration route (oral, intravenous, topical).

[l] Adverse events and serious adverse events that occur after the patient has signed the informed consent form (ICF) through 30 days after the last dose of IMLYGIC will be recorded in the electronic case report form (eCRF). Adverse events should be assessed on an ongoing basis.

[m] Safety events which are considered serious must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator's awareness.

[n] Adverse events and serious adverse events that occur more than 30 days after the last dose of IMLYGIC and deemed by the Investigator to be related to treatment with IMLYGIC. **Any fatal outcome during long term follow up should be reported as a serious adverse event.**

[o] Product complaints that occur after the patient has signed the ICF through 30 days after the last dose of IMLYGIC.

[p] Other safety findings include, for example, medication errors, exposure to IMLYGIC during pregnancy and breastfeeding, accidental exposure, that occur after the patient has signed the ICF through 30 days after the last dose of IMLYGIC.

[q] Record the following information on survival status: date of contact, status (eg, alive or deceased), and date and cause of death (if applicable).

[r] If patients, their close contacts, or their health care providers suspect the presence of herpetic infection, it will be evaluated according to the standard of care for IMLYGIC as described in the IMLYGIC United States Prescribing Information and the Summary of Product Characteristics. **The swab will be provided by a specialized laboratory (Viracor) which will test for the presence of IMLYGIC® DNA. In order to collect a viable sample in a timely manner, testing swabs from the HCP's office can also be used as long as swabs meet the following criteria: flocked fiber swabs, tip size regular or standard, shaft must NOT be wood, in sterile dry transport tube. Please refer to the list of acceptable swabs shown in Appendix 1 of the laboratory manual if unsure if the appropriate swab is being used or need to request a swab for qPCR testing.**

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## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| CTCAE | Common Terminology Criteria for Adverse Events |
| eCRF | electronic case report form |
| ECOG | Eastern Cooperative Oncology Group |
| EDC | electronic data capture |
| GM-CSF | human granulocyte macrophage colony-stimulating factor |
| HCP | health care provider |
| HSV-1 | herpes simplex virus type 1 |
| ICF | informed consent form |
| ICP | infected cell protein |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PFU | plaque-forming unit |
| qPCR | quantitative polymerase chain reaction |
| SmPC | Summary of Product Characteristics |
| USPI | United States Prescribing Information |

## 3. RESPONSIBLE PARTIES

PPD

Center for Observational Research

PPD

## 4. ABSTRACT

- **Study Title**

A Postmarketing Prospective Cohort Study of Melanoma Patients Treated With IMLYGIC® (Talimogene Laherparepvec) in Clinical Practice to Characterize the Risk of Herpetic Infection Among Patients, Close Contacts, and Health Care Providers; and Long-term Safety in Treated Patients

- **Study Background and Rationale**

IMLYGIC is an oncolytic viral therapy that is approved for use in certain adults with unresectable melanoma. IMLYGIC is an attenuated herpes simplex virus type 1 (HSV-1) that was derived by functional deletion of 2 genes (infected cell protein 34.5 [ICP34.5] and ICP47) and insertion of the coding sequence for human granulocyte macrophage colony-stimulating factor (GM-CSF). The viral nature of IMLYGIC presents the potential risks of primary herpetic infection by IMLYGIC during treatment and reactivation from latent state after treatment among patients, as well as the potential risks of stimulating reactivation of latent wild-type HSV-1 in patients and of secondary transmission and infection by IMLYGIC among patient's close contacts and health care providers (HCPs). Herpetic infection may present clinically as oral or genital herpes, herpetic whitlow or herpetic gladiatorum of the skin, ocular herpes, herpetic encephalitis, and disseminated herpetic infection. To characterize these potential risks, this postmarketing prospective cohort study will follow a cohort of melanoma patients during and after treatment with IMLYGIC for up to 5 years and monitor for the potential viral transmission to their close contacts and HCPs through the existing Postmarketing IMLYGIC Surveillance Program. This study is an FDA Post Marketing Requirement #1 (PMR #1) under the pharmacovigilance plan and listed as category 3 according to the European Union Risk Management Plan.

- **Research Question and Objectives**
  - Primary Objective

  - Estimate the incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients for up to 5 years after the first IMLYGIC dose

- Secondary Objectives
  - Count the number of herpetic infections with detection of talimogene laherparepvec DNA among close contacts and HCPs**.**
  - Estimate the incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients during treatment with IMLYGIC.
  - Estimate the incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients after discontinuation of IMLYGIC.
  - Estimate the incidence rate of herpetic infection with detection of wild-type HSV-1 among patients during treatment with IMLYGIC.
  - Estimate the incidence rate of herpetic infection with detection of wild-type HSV-1 among patients after discontinuation of IMLYGIC.
  - Describe patient characteristics.
  - Describe the use of IMLYGIC, other anticancer therapy, antiherpetic therapy.
  - Describe adverse events and serious adverse events**.**
  - Describe overall survival.

- Hypothesis/Estimation

  This study is descriptive in nature and no formal hypothesis will be tested. The study will estimate the incidence rate of herpetic infection.

- **Study Design**

This postmarketing prospective cohort study will follow melanoma patients for up to 5 years after the first IMLYGIC dose in clinical practice. There is no experimental intervention, and the study population will receive standard-of-care treatment as determined by their treating physician.

- **Study Population**

Study enrollment will be offered to patients meeting eligibility criteria at participating medical sites. The number of study sites will depend on IMLYGIC use during the study enrollment (beginning in Q3 2017).

- **Summary of Patient Eligibility Criteria**
  - Inclusion criteria
    - Patient has provided written informed consent.
    - Patient is an adult (≥ 18 years of age at the time of informed consent) with a diagnosis of melanoma.

- Patient enrolled within 1 month of receiving the first dose of IMLYGIC for the treatment of melanoma.

– Exclusion criteria

- Patient has a prior history of being a subject in an interventional clinical trial for IMLYGIC.

- **Follow-up**

The patient's follow-up begins at enrollment and continues through the earliest date of: 5 years after the first IMLYGIC dose, death, withdrawal of consent, or loss to follow-up. Study assessments are detailed in the Table 1. During IMLYGIC treatment, the study assessments for signs and symptoms of herpetic infection, safety, and survival are to be completed at the clinic visits for IMLYGIC treatment. After discontinuation of IMLYGIC until the end of follow-up, these study assessments are to be completed every 3 months (± 30 days) via phone or routine clinic visits if they fall within the 30-day window. Data collected will be transcribed into an electronic case report form (eCRF).

At any time that enrolled patients, their close contacts, or their HCPs develop a suspected herpetic lesion, they should seek medical attention to evaluate and swab any suspicious lesion for talimogene laherparepvec DNA testing (per the Postmarketing IMLYGIC Surveillance Program) or wild-type HSV-1 testing (per local standard of care) (Centers for Disease Control, 2010; Patel et al, 2010). The evaluation and reporting of suspected herpetic infections will be done according to the standard of care for IMLYGIC as described in the IMLYGIC United States Prescribing Information (USPI) and the Summary of Product Characteristics (SmPC). In addition to these materials, for this study, patients will receive an information sheet about the study to share with their close contacts and HCPs. This information sheet will describe the study and will contain the study number for use in reporting a suspected herpetic infection.

For patients enrolled in this study, informed consent will be collected upon study enrollment to link test results from the existing Postmarketing IMLYGIC Surveillance Program to the patient (see Appendix E for a sample laboratory report from Viracor). The results will be captured in the eCRF and be included in the data analysis of the study. For close contacts and HCPs, test results from the Postmarketing IMLYGIC Surveillance Program will be linked to the study only and not to any identifiable patient information, such as the name or date of birth.

- **Variables**

Endpoints/Outcomes

- Primary Endpoint
  - Incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients. Herpetic infection includes oral herpes, genital herpes, herpetic whitlow or herpetic gladiatorum of the skin, ocular herpes, herpetic encephalitis, and disseminated herpetic infection.

- Secondary Endpoints
  - Count of herpetic infections with detection of talimogene laherparepvec DNA among close contacts and HCPs
  - Incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients during treatment with IMLYGIC
  - Incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients after discontinuation of IMLYGIC
  - Incidence rate of herpetic infection with detection of wild-type HSV-1 among patients during treatment with IMLYGIC
  - Incidence rate of herpetic infection with detection of wild-type HSV-1 among patients after discontinuation of IMLYGIC
  - Summary of patient characteristics
  - Treatment patterns of anticancer therapy (eg, types and sequence)
  - Incidence of use of antiherpetic therapy
  - Incidence of adverse events and serious adverse events during treatment with IMLYGIC
  - Incidence of adverse events and of serious adverse events related to IMLYGIC after discontinuation of IMLYGIC
  - Overall survival

Exposure

- Total cumulative dose and duration of IMLYGIC treatment

- **Study Sample Size**

1. The total number of patients who will participate in this study will be determined by the number of patients with postmarket use of IMLYGIC who consent to and are deemed eligible to participate in this study. For a sample size to provide an 80% probability of detecting a true event rate of 3 herpetic infections with detection of talimogene laherparepvec DNA per 1000 patients-years, 535 patient-years of follow-up are needed. To observe 535 patient-years, accounting for a 5-year study and length of follow-up based on historical mortality data (~2 years mean duration of survival) and because patients may withdraw consent, the projected total number of patients needed to enroll is estimated to be approximately 300. Based upon observed loss to follow-up of the first

82 patients enrolled (6%), the projected enrollment number is adjusted to complete study with 535 patient-years. If no events of herpetic infection with detection of talimogene laherparepvec DNA occur, the precision at the upper 95% confidence level for the true incidence rate is 6.9 events per 1000 patient-years.

- **Data Analysis**

The statistical analysis will be entirely descriptive and no formal hypothesis will be tested.

## 5. AMENDMENTS AND UPDATES

| Amendment or Update Number | Date | Amendment or Update |
|---|---|---|
| Protocol Amendment 1 | 28 July 2016 | See Summary of Changes |
| Protocol Amendment 2 | 12 April 2017 | See Summary of Changes |
| Protocol Amendment 3 | 03 September 2020 | See Summary of Changes |
| Protocol Amendment 4 | 26 August 2021 | See Summary of Changes |
| Protocol Amendment 5 | 25 August 2022 | See Summary of Changes |
| **Superseding Protocol Amendment 5** | **12 October 2022** | **See Summary of Changes** |

## 6. RATIONALE AND BACKGROUND

### 6.1 Diseases and Therapeutic Area

Globally, an estimated 49,100 people die of melanoma annually, and more than one-half of these deaths occur in North America and Europe (Lozano et al, 2012). The 5-year survival, which was calculated based on information from several major medical centers, ranges from 59% for stage IIIB to 5% for stage IV M1c (Balch et al, 2009).

Since 2011, the range of therapeutic options for metastatic melanoma has significantly expanded with 6 new agents approved within 2 therapeutic classes: immunotherapies (ipilimumab, pembrolizumab, nivolumab) and BRAF- or MEK-targeted therapies (vemurafenib, dabrafenib, trametinib). Treatment combinations, including ipilimumab plus nivolumab and dabrafenib plus trametinib, are also approved options.

IMLYGIC® (talimogene laherparepvec) is an intralesionally administered oncolytic immunotherapy derived from attenuated herpes simplex virus type 1 (HSV-1) by functional deletion of 2 genes (infected cell protein 34.5 [ICP34.5] and ICP47) and insertion of the coding sequence for human granulocyte macrophage colony-stimulating factor (GM-CSF). The ICP34.5 deletion allows the virus to replicate selectively in

tumors, and the deletion of ICP47 leads to antigen presentation to major histocompatibility complex class I and II molecules. The latter deletion also allows the increased expression of the US11 gene that promotes virus growth in cancer cells without decreasing tumor selectivity. Finally, the presence of GM-CSF allows stimulation of cellular immune responses. IMLYGIC has received regulatory approval in the United States**,** European Union**,** and other countries for their respective indications in the treatment of unresectable melanoma.

IMLYGIC is administered by injection into injectable cutaneous, subcutaneous, and nodal lesions that are visible, palpable, or detectable by ultrasound guidance. IMLYGIC is provided in single-use vials of 1 mL each in 2 different dose strengths: $10^6$ (1 million) plaque-forming units (PFU) per mL for the initial treatment visit only and $10^8$ (100 million) PFU per mL for all subsequent treatment visits. The total injection volume for each treatment visit should not exceed 4 mL for all injected lesions combined. The recommended dosing schedule is as follows: the initial treatment visit, the second treatment visit at 3 weeks after the initial treatment, and all subsequent treatment visits at 2-week intervals. IMLYGIC treatment is continued for at least 6 months unless other treatment is required or until there are no injectable lesion. IMLYGIC treatment can be reinitiated if new unresectable cutaneous, subcutaneous, or nodal lesions appear after a complete response.

### 6.2 Rationale

Wild-type HSV-1, the parent virus of IMLYGIC, is commonly acquired during childhood, and seroprevalence in the United States is 54% among persons aged 14 to 49 years (Bradley et al, 2014) and 63% among pregnant women (Xu et al, 2007). HSV-1 is transmitted by direct contact with the mucocutaneous surfaces of an infected person. Most signs and symptoms present near the site of infection. The most common manifestation of HSV-1 infection is cold sores at the mucocutaneous junction. While typically the site of infection is oral or genital mucosa, the site can include other regions where there is contact exposure. Examples include herpetic whitlow on finger of dental professionals (Browning and McCarthy, 2012) and herpetic gladiatorum on the face and periorbital region of wrestling athletes (Anderson, 2003). While lesions are most likely to occur near the time of initial exposure, herpes viruses are known to establish latency in the regional neural root ganglia; and recurrences, typically in the same region, may occur over subsequent years (Engelberg et al, 2003). Fever, stress, and other factors

are common triggers of recurrence. Frequent recurrences of cold sores are reported by 3% to 5% of the general population (Rooney et al, 1993).

HSV-1 infection may also include ocular HSV-1 infection, occurring at an incidence of 8 to 13 per 100,000 in the general population (Young et al, 2010). Ocular HSV-1 may present as herpetic conjunctivitis, keratitis, or uveitis. Life-threatening HSV-1 infections include herpetic encephalitis, occurring at an incidence of 1 to 3 per million (Hjalmarsson et al, 2007), and disseminated HSV-1 infection with fulminant multi-organ failure. Most case reports of disseminated HSV-1 infection are among immunocompromised persons, but may also occur in immunocompetent persons (Norvell et al, 2007; Watanabe et al, 2010). HSV-1 is generally not considered an opportunistic infection among immunocompromised persons. For example, human immunodeficiency virus (HIV) positive and HIV-negative men have a similar HSV-1 seroprevalence (Russell et al, 2001; Smit et al, 2007). However, immunocompromised persons with HSV-1 have more frequent recurrences and severe clinical manifestations than the general population with HSV-1 (Zuckerman et al, 2009).

An important and logical consideration in the use of IMLYGIC is the potential risk of primary infection and reactivation of the virus in patients, as well as the risk of viral transmission from patients to close contacts (close contacts include household members, caregivers, sex partners, and persons sharing the same bed) and HCPs. To assess this risk, preclinical and clinical studies have assessed the biodistribution and shedding, as well as potential for transmission of IMLYGIC. In preclinical models, the biodistribution of IMLYGIC appears to be predominantly restricted to tumor, blood, and tissues that may be associated with immune-mediated viral clearance (spleen, lymph node, liver). In the clinical setting, biodistribution and shedding were initially studied in the first-in-human study (Hu et al, 2006); in this study viral DNA was never detected outside of the occlusive dressing. No viral DNA was detectable in either blood or urine past 1 week after each dose.

Furthermore, biodistribution and shedding of IMLYGIC in IIIB and IVM1c melanoma patients was investigated in a phase 2, single-arm study. The final analysis showed that consistent with the method of administration, talimogene laherparepvec DNA was detected with greatest frequency in swabs of injected lesions (49% of samples in 100% of subjects) and blood (35% of samples in 98% of subjects). Live virus was not detected among 1085 swabs of the exterior of occlusive dressings. Thirty-seven swabs of lesions suspected herpetic origin were taken from 19 subjects, 4 swabs from 3 subjects had

detectable talimogene laherparepvec DNA, but all were negative for viral infectivity by TCID50 assay (www.clinicaltrials.gov, NCT02014441).

Consistent with the above findings, among study subjects in the clinical trials to date, no cases of confirmed symptomatic herpetic infection or cases of secondary transmission from IMLYGIC have been reported. During the phase 3 registrational study, 16 herpetic events were reported among subjects who received IMLYGIC; 14 events were reported as cold sores, one as HSV-1 infection, and one as herpetic keratitis. However, none of these lesions were tested for IMLYGIC, and there was no pathologic confirmation of a herpetic infection. For additional information, please refer to the IMLYGIC Investigator's Brochure.

Although no cases of confirmed symptomatic herpetic infection from IMLYGIC have been reported to date, a potential risk to the patient is the risk for primary infection during treatment and reactivation from latent state after treatment due to the viral nature of IMLYGIC. Furthermore, another possible risk recognized by both Amgen and regulatory authorities is the potential reactivation of latent wild-type HSV-1 by IMLYGIC (eg, febrile response to IMLYGIC) which would increase the rate of infection by wild-type HSV-1. Lastly, secondary transmission and infection to the patient's close contacts and health care providers (HCPs) is a recognized potential risk. To further characterize these potential risks, this postmarketing prospective cohort study will follow a cohort of patients for up to 5 years after the first dose of IMLYGIC and monitor for herpetic infection in patients and for viral transmission to close contacts and HCPs through the existing Postmarketing IMLYGIC Surveillance Program. This study is an FDA Post Marketing Requirement #1 (PMR #1) and is listed as category 3 measure according to the European Union Risk Management Plan.

### 6.3 Statistical Inference (Estimation or Hypothesis)

This study is descriptive in nature and no formal hypothesis will be tested. The study will estimate the incidence rate of herpetic infection.

## 7. RESEARCH QUESTION AND OBJECTIVES

### 7.1 Primary Objectives

- Estimate the incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients for up to 5 years after the first IMLYGIC dose.

### 7.2 Secondary Objectives

- Count the number of herpetic infections with detection of talimogene laherparepvec DNA among close contacts and HCPs.

- Estimate the incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients during treatment with IMLYGIC.
- Estimate the incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients after discontinuation of IMLYGIC.
- Estimate the incidence rate of herpetic infection with detection of wild-type HSV-1 among patients during treatment with IMLYGIC.
- Estimate the incidence rate of herpetic infection with detection of wild-type HSV-1 among patients after discontinuation of IMLYGIC.
- Describe patient characteristics.
- Describe the use of IMLYGIC, other anticancer therapy, antiherpetic therapy.
- Describe adverse events and serious adverse events.
- Describe overall survival.

## 8. RESEARCH METHODS

### 8.1 Study Design

This postmarketing prospective cohort study will follow melanoma patients for up to 5 years after the first IMLYGIC dose in clinical practice. There is no experimental intervention, and the study population will receive standard-of-care treatment as determined by their treating physician.

### 8.2 Setting and Study Population

#### 8.2.1 Study Period

Study enrollment for Study 20130193 began in 2017. The study period will end after the last patient enrolled has had the opportunity to contribute 5 years of observation from the first dose of IMLYGIC.

#### 8.2.2 Selection and Number of Sites

Study sites for Study 20130193 will include up to 35 medical centers that have postmarket use of IMLYGIC and a Principal Investigator who is interested in observational research. Study enrollment will be offered to patients meeting eligibility criteria at participating medical centers.

#### 8.2.3 Patient Eligibility

Study participants shall be referred to as patients. Criteria are designed to best reflect IMLYGIC use in real-world, clinical practice.

##### 8.2.3.1 Inclusion Criteria

- Patient has provided written informed consent.
- Patient is an adult (≥ 18 years of age at the time of informed consent) with a diagnosis of melanoma.

- Patient enrolled within 1 month of receiving the first dose of IMLYGIC for the treatment of melanoma.

#### 8.2.3.2 Exclusion Criteria

- Patient has a prior history of being a subject in an interventional clinical trial for IMLYGIC.

### 8.2.4 Baseline Period

The baseline assessment will be completed at clinic visit for administration of IMLYGIC. Study assessments are described in detail in Table 1.

### 8.2.5 Study Follow-up

The patient's follow-up begins at enrollment and continues through the earliest date of: 5 years after the first IMLYGIC dose, death, withdrawal of consent, or loss to follow-up. Study assessments are detailed in the Table 1. During IMLYGIC treatment, the study assessments for signs and symptoms of herpetic infection, safety, and survival are to be completed at the clinic visits for IMLYGIC treatment. After discontinuation of IMLYGIC until the end of follow-up, these study assessments are to be completed every 3 months (± 30 days) via phone or routine clinic visits if they fall within the 30-day window. Data collected will be transcribed into an electronic case report form (eCRF).

At any time that enrolled patients, their close contacts, or their HCPs develop a suspected herpetic lesion, they should seek medical attention to evaluate and swab any suspicious lesion for talimogene laherparepvec DNA testing (per the Postmarketing IMLYGIC Surveillance Program) or wild-type HSV-1 testing (per local standard of care) (Centers for Disease Control, 2010; Patel et al, 2010). The evaluation and reporting of suspected herpetic infections will be done according to the standard of care for IMLYGIC as described in the IMLYGIC USPI and the SmPC. In addition to these materials, for this study, patients will receive an information sheet about the study to share with their close contacts and HCPs. This information sheet will describe the study and will contain the study number for use in reporting a suspected herpetic infection.

For patients enrolled in this study, informed consent will be collected upon study enrollment to link test results from the existing Postmarketing IMLYGIC Surveillance Program to the patient (see Appendix E for a sample laboratory report from Viracor). The results will be captured in the eCRF and be included in the data analysis of the study. For close contacts and HCPs, test results from the Postmarketing IMLYGIC Surveillance Program will be linked to the study only and not to any identifiable patient information, such as the name or date of birth.

Subjects who have ended IMLYGIC treatment and entered into the follow-up period may be allowed to restart treatment if the investigator chooses. In such cases, after restarted IMLYGIC treatment is ended, subjects will continue in the follow-up period as outlined in the schedule of assessments.

## 8.3 Variables

### 8.3.1 Exposure Assessment

The use of IMLYGIC will be characterized in two ways: duration of therapy (in days) and in total cumulative dose.

### 8.3.2 Outcome Assessment

#### 8.3.2.1 Primary Endpoint

- Incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients Herpetic infection includes oral herpes, genital herpes, herpetic whitlow or herpetic gladiatorum of the skin, ocular herpes, herpetic encephalitis, and disseminated herpetic infection.

For either swab samples or appropriate biological sample for disseminated infection, a specialty laboratory will use a quantitative polymerase chain reaction (qPCR) test that is specific for talimogene laherparepvec DNA. Results will be reported as detectable talimogene laherparepvec DNA levels. The incidence rate will be summarized for detectable DNA results during follow-up.

#### 8.3.2.2 Secondary Endpoints

- Count of herpetic infections with detection of talimogene laherparepvec DNA among close contacts and HCPs

Herpetic infection includes oral or genital herpes, herpetic whitlow or herpetic gladiatorum of the skin, ocular herpes, herpetic encephalitis, and disseminated herpetic infection. For either swab samples or appropriate biological sample for disseminated infection, a specialty laboratory will use a qPCR test that is specific for talimogene laherparepvec DNA. Results will be reported as detectable talimogene laherparepvec DNA levels.

- Incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients during treatment with IMLYGIC

The incidence rate will be summarized for detectable talimogene laherparepvec DNA results from the date of first IMLYGIC dose to the date of last IMLYGIC dose + 30 days. If patients receive IMLYGIC over multiple treatment phases, the treatment period is defined as the sum of time from the date of first IMLYGIC dose to 30 days after the date

of last IMLYGIC dose or the day before the subsequent treatment phase, whichever comes first, in each treatment phase.

- Incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients after discontinuation of IMLYGIC

The incidence rate will be summarized for detectable talimogene laherparepvec DNA results during the period from 31 days after the last dose of IMLYGIC through the end of follow-up. If patients receive IMLYGIC over multiple treatment phases, each post-treatment period is defined as sum of time from 31 days after date of last IMLYGIC dose in the prior treatment phase to 1 day prior to the date the first IMLYGIC dose in the subsequent treatment phase or the end of study.

- Incidence rate of herpetic infection with detection of wild-type HSV-1 among patients during treatment with IMLYGIC

For either swab samples or appropriate biological sample for suspected herpetic infection, tests that are specific for wild-type HSV-1 should be performed per local standard of care (Centers for Disease Control, 2010; Patel et al, 2010). Results will be reported as either positive or negative for HSV-1.

The incidence rate will be summarized for positive tests occurring from the date of first IMLYGIC dose to the date of last IMLYGIC dose + 30 days. If patients receive IMLYGIC over multiple treatment phases, the treatment period is defined as the sum of time from the date of first IMLYGIC dose to 30 days after the date of last IMLYGIC dose or the day before the subsequent treatment phase, whichever comes first, in each treatment phase.

- Incidence rate of herpetic infection with detection of wild-type HSV-1 among patients after discontinuation of IMLYGIC

The incidence rate will be summarized for positive tests occurring from 31 days after the last dose of IMLYGIC through the end of follow-up. If patients receive IMLYGIC over multiple treatment phases, each post-treatment period is defined as sum of time from 31 days after date of last IMLYGIC dose in the prior treatment phase to one day prior to the date of the first IMLYGIC dose in the subsequent treatment phase or the end of study.

- Summary of patient characteristics

The following baseline variables will be recorded: sex, age, **race, ethnicity,** Eastern Cooperative Oncology Group (ECOG) performance status, and disease stage.

- Treatment patterns of anticancer therapy (eg, types and sequence)

For more detail on what types of anticancer therapies will be recorded, please refer to footnote “f” in Table 1.

- Incidence of use of antiherpetic therapy

For more detail on what types of antiherpetic therapy will be recorded, please refer to footnote “k” in Table 1 .

- Incidence of adverse events and serious adverse events during treatment with IMLYGIC

Adverse events and serious adverse events (as defined in Section 11) that occur from the date of first IMLYGIC dose to the date of last IMLYGIC dose + 30 days. If patients receive IMLYGIC over multiple treatment phases, the adverse events and serious adverse events collection period is defined as the date of first IMLYGIC dose to 30 days after the date of last IMLYGIC dose or the day before the subsequent treatment phase, whichever comes first, in each treatment phase.

- Incidence of adverse events and serious adverse events related to IMLYGIC after discontinuation of IMLYGIC

Adverse events and serious adverse events (as defined in Section 11) that occur more than 31 days after the last dose of IMLYGIC and attributed to IMLYGIC by the physician.

If patients receive IMLYGIC over multiple treatment phases, the adverse events and serious adverse events collection period is defined as 31 days after date of last IMLYGIC dose in the prior treatment phase to one day prior to the date of the first IMLYGIC dose in the subsequent treatment phase or the end of study.

- Overall survival

Survival is defined by the time to death from the date of the first use of IMLYGIC. Patients who are alive or lost to follow-up at the time of the analysis will be censored.

### 8.3.3 Validity and Reliability

The process for collection of samples for qPCR testing of talimogene laherparepvec DNA among patients, close contacts, and HCPs will follow the Prescribing Information approved by the local health authorities. Further details are available in the Post-Marketing Instruction Manual for IMLYGIC Surveillance Program.

### 8.4 Data Sources

Screening, baseline, and follow-up patient data will be transcribed into the eCRF whenever possible.

### 8.5 Study Size

The total number of patients who will participate in this study will be determined by the number of patients with post-market use of IMLYGIC who consent to and are deemed eligible to participate in this study. For a sample size to provide an 80% probability of detecting a true event rate of 3 herpetic infections with detection of talimogene laherparepvec DNA per 1000 patients-years, 535 patient-years of follow-up are needed (Table 2). To observe 535 patient-years, accounting for a 5-year study and length of follow-up based on historical mortality data (~2 years mean duration of survival), and because patients may withdraw consent, the projected total number of patients needed to enroll is estimated to be approximately 300. Based upon observed loss to follow-up of the first 82 patients enrolled (6%), the projected enrollment number is adjusted to complete study with 535 patient-years. If no events of herpetic infection with detection of talimogene laherparepvec DNA occur, the precision at the upper 95% confidence level for the true incidence rate is 6.9 events per 1000 patient-years.

**Table 2. Statistical Power Provided by Enrollment Target Scenarios**

| Patient-years of follow-up in 5-year study | If true event rate is 1 per 1000 patient-years, probability that at least one event will be observed[a] | Upper confidence bound of events per 1000 patient-years if 0 events observed[b] | Projected number of patients to enroll to obtain patient-years of follow-up | |
|---|---|---|---|---|
| | | | 2-year patient survival[c] | 3-year patient survival[d] |
| 275 | 56% | 13.4 | 154 | 108 |
| 350 | 65% | 10.5 | 196 | 138 |
| 475 | 76% | 7.8 | 266 | 187 |
| 535 | 80% | 6.9 | 300 | 210 |
| 650 | 86% | 5.7 | 364 | 256 |

[a] Model of rare events for Poisson distribution with parameter = > 0, if for k = 0, 1, 2,... the probability to observe k events is given by:

$$\Pr(X = k) = \frac{(\lambda m)^k e^{-(\lambda m)}}{k!}$$

Where λ is the event rate, m is the number of patient-years, the chance of observing k or more events is:

$$1 - \Pr(X \leq k - 1)$$

[b] Standard one-tailed 97.5% confidence interval from the Poisson distribution, available at: handbook.cochrane.org/chapter_16/16_9_4_confidence_intervals_when_no_events_are_observed.htm

[c] Assumes patient survival of 2 years, plus 15% more patients for additional loss to follow-up.
[d] Assumes patient survival of 3 years, plus 15% more patients for additional loss to follow-up.

## 8.6 Data Management

### 8.6.1 Obtaining Data Files

Data capture is planned to be electronic:

**Patients**

- Each patient will be assigned a unique identification number at enrollment.
- Data from patients will be entered by site staff into an electronic database provided by the sponsor.

**Close contacts and HCPs**

- Data will be acquired from the Postmarketing IMLYGIC Surveillance Program.

Amgen representative(s) are responsible for contacting and visiting the Investigator for the purpose of inspecting various records of the study (eg, eCRFs and other pertinent data), provided that patient confidentiality is respected.

The Clinical Monitor or designee is responsible for checking entries in the eCRFs at regular intervals throughout the study to verify adherence to the protocol as well as the completeness, accuracy, and consistency of the data. In accordance with local laws and regulations, the Clinical Monitor or designee is to have access to patient medical records and other study-related records that are needed to verify entries on the eCRFs.

The Investigator agrees to cooperate with the Clinical Monitor or designee to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

### 8.6.2 Review and Verification of Data Quality

Upon receipt of data from study sites, Amgen will check the data for potential errors and inconsistencies. The data will be evaluated for potential outliers, missing information, and logical consistency with the study variables. Sites will be queried for clarification if unlikely values, potential errors, or inconsistencies are identified.

## 8.7 Data Analysis

### 8.7.1 Planned Analyses

#### 8.7.1.1 Interim Analyses

During data collection, annual study progress reports will be completed for inclusion in Periodic Safety Update Reports. These interim analyses will report on study recruitment (eg, number of patients enrolled), study conduct (eg, patient-years of observation), and

the primary and secondary endpoints assessed at that point in time. Additional ad hoc analysis may be conducted if required for submission to regulatory authorities.

#### 8.7.1.2 Final Analysis

The final analysis will be completed once all enrolled patients have had the opportunity to contribute 5 years of observation.

### 8.7.2 Planned Method of Analysis

#### 8.7.2.1 General Considerations

This study is descriptive in nature and no formal hypothesis will be tested. Select summaries will also be presented **by** region.

This study will estimate incidence rate of herpetic infection. The incidence rate will be calculated as the number of events divided by sum of follow-up time in patient-years.

#### 8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Missing data will not be imputed.

Lost to follow-up will be characterized by median duration of observation for study population and reasons for loss to follow-up will be tabulated (mortality, no response from patient, withdraw of consent, or other).

#### 8.7.2.3 Descriptive Analysis

##### 8.7.2.3.1 Description of Study Enrollment

Based on the numeric tally of patients in screening log, the proportion of patients enrolling in the study will be summarized.

To describe if study patients are representative of the broader population of IMLYGIC patients, all patients in the screening log and the study patients will be reported by proportion for these variables: sex, age, **race, ethnicity,** and disease stage.

##### 8.7.2.3.2 Description of Patient Characteristics

The study population will be characterized by sex, age, **race, ethnicity,** ECOG performance status, disease stage, history of herpetic infections, and previous melanoma therapy.

#### 8.7.2.4 Analysis of the Primary and Secondary Endpoints

##### 8.7.2.4.1 Analysis of the Primary Endpoint

- Incidence of herpetic infection with detection of talimogene laherparepvec DNA among patients. Herpetic infection includes oral herpes, genital herpes, herpetic whitlow or herpetic gladiatorum of the skin, ocular herpes, herpetic encephalitis, and disseminated herpetic infection.

The incidence rate will be calculated as the number of suspected herpetic infections that are detectable for talimogene laherparepvec DNA divided by sum of follow-up time (last date of follow-up minus the date of first IMLYGIC dose) in patient-years. As a measure of precision, a 95% confidence interval will be calculated around the incidence rate.

#### 8.7.2.4.2 Analysis of the Secondary Endpoints

- Count of herpetic infections with detection of talimogene laherparepvec DNA among close contacts and HCPs

Separate counts will be reported for the number of suspected herpetic infections that are detectable for talimogene laherparepvec DNA in close contacts and HCPs.

- Incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients during treatment with IMLYGIC

The incidence rate will be calculated as the number of suspected herpetic infections that are detectable for talimogene laherparepvec DNA divided by sum of follow-up time during treatment period with IMLYGIC dose. If patients receive IMLYGIC over multiple treatment phases, the treatment period is defined as the sum of time from the date of first IMLYGIC dose to 30 days after the date of last IMLYGIC dose or the day before the subsequent treatment phase, whichever comes first, in each treatment phase in patient-years. As a measure of precision, a 95% confidence interval will be calculated around the incidence rate.

- Incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients after discontinuation of IMLYGIC

The incidence rate will be calculated as the number of suspected herpetic infections that are detectable for talimogene laherparepvec DNA divided by sum of follow-up time after discontinuation of IMLYGIC (last date of follow-up minus the date of last IMLYGIC dose plus 31 days). If patients receive IMLYGIC over multiple treatment phases, each post-treatment period is defined as sum of time from 31 days after date of last IMLYGIC dose in the prior treatment phase to one day prior to the date of the first IMLYGIC dose in the subsequent treatment phase or the end of study in patient-years. As a measure of precision, a 95% confidence interval will be calculated around the incidence rate.

- Incidence rate of herpetic infection with detection of wild-type HSV-1 among patients during treatment with IMLYGIC

The incidence rate will be calculated as the number of suspected herpetic infections that test positive for wild-type HSV-1 divided by sum of follow-up time during treatment period with IMLYGIC (the date of last IMLYGIC dose plus 30 days minus the date of first

IMLYGIC dose). If patients receive IMLYGIC over multiple treatment phases, the treatment period is defined as the sum of time from the date of first IMLYGIC dose to 30 days after the date of last IMLYGIC dose or the day before the subsequent treatment phase, whichever comes first, in each treatment phase in patient-years. As a measure of precision, a 95% confidence interval will be calculated around the incidence rate.

- Incidence rate of herpetic infection with detection of wild-type HSV-1 among patients after discontinuation of IMLYGIC

The incidence rate will be calculated as the number of suspected herpetic infections that test positive for wild-type HSV-1 divided by sum of follow-up time (last date of follow-up minus the date of last IMLYGIC dose plus 31 days). If patients receive IMLYGIC over multiple treatment phases, each post-treatment period is defined as sum of time from 31 days after date of last IMLYGIC dose in the prior treatment phase to one day prior to the date of the first IMLYGIC dose in the subsequent treatment phase or the end of study in patient-years. As a measure of precision, a 95% confidence interval will be calculated around the incidence rate.

- Summary of patient characteristics

Demographic and clinical characteristics will be summarized using categorical (n and %) and continuous statistics (n, mean, standard deviation, median, quartiles, minimum and maximum).

- Treatment patterns of anticancer therapy (eg, types and sequence)

The number, types, and order of treatments received will be reported.

- Incidence of use of antiherpetic therapy

Patient incidence (n and %) of use of antiherpetic therapy will be reported.

- Incidence of adverse events and serious adverse events during treatment with IMLYGIC

Patient incidence (n and %) of adverse events and serious adverse events occurring between the date of first IMLYGIC dose and the date of last IMLYGIC dose plus 30 days will be reported. If patients receive IMLYGIC over multiple treatment phases, the adverse events and serious adverse events collection period is defined as the date of first IMLYGIC dose to 30 days after the date of last IMLYGIC dose or the day before the subsequent treatment phase, whichever comes first, in each treatment phase

- Incidence of adverse events and of serious adverse events related to IMLYGIC after the treatment period with IMLYGIC

Patient incidence (n and %) of adverse events and serious adverse events occurring after the date of last IMLYGIC dose plus 31 days will be reported. If patients receive IMLYGIC over multiple treatment phases, the adverse events and serious adverse events collection period is defined as 31 days after date of last IMLYGIC dose in the prior treatment phase to one day prior to the date of the first IMLYGIC dose in the subsequent treatment phase or the end of study.

- Overall survival

Overall survival will be estimated using the Kaplan-Meier method with the time to death being calculated from the date of the first IMLYGIC dose.

Patients who are alive or lost to follow-up at the time of the analysis will be censored.

#### 8.7.2.4.3 Subgroup Analysis

The primary endpoint will be presented by variables that may relate to occurrence of primary endpoint, including:

- age
- **sex**
- **race**
- **ethnicity**
- history of herpetic infections (yes or no)

### 8.7.3 Analysis of Safety Endpoints/Outcomes

Details of the analyses of safety endpoints are outlined in Section 8.7.2.4.2.

The Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or later will be used to code all adverse events.

## 8.8 Quality Control

The Investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries or corrections on eCRFs will be included on the Amgen Delegation of Authority Form. The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen or applicable regulatory authorities.

Documents to be maintained for the study are as follows:

- Patient's files containing the completed eCRF, patient identification list, and informed consent forms (ICFs), as applicable.

- Study files containing the protocol with all amendments, copies of prestudy documentation, and all correspondence to and from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
- All source documentation supporting entries into the eCRFs must be maintained and available upon request.
- Source documents are original documents, data, and records from which the patient's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.
- Retention of study documents will be governed by the contractual agreement with Amgen.
- Additional steps of quality control are:
  - The sponsor will provide protocol-specific training to all site staff; additionally, a completion guide for the eCRF will be provided.
  - Updates to eCRFs will be automatically documented through the software's "audit trail".
  - The Investigator signs only the Investigator Verification Form for this electronic data capture (EDC) study. The signature indicates that the Investigator inspected or reviewed the data on the CRF and agrees with the content.

## 8.9 Limitations of the Research Methods

### 8.9.1 Internal Validity of Study Design

Identification of the primary endpoint, incidence rate of herpetic infection with detection of talimogene laherparepvec DNA among patients enrolled in Study 20130193 may be susceptible to measurement error because suspected cases of herpetic infection in the real world may be infrequently brought to medical attention. Herpetic infection data retrieved from the study will be collected in a rigorous manner, and the patients themselves will be an important source of information. Targeted education and training linked to the Prescribing Information will ensure that patients and Investigators are aware of the signs and symptoms that may indicate herpetic infection and of the need for timely reporting for sample collection. These study procedures for identifying herpetic infection are built upon approaches for data collection within clinical studies of herpes simplex vaccine (Belshe et al, 2012), natural history studies of HSV (Mark et al, 2008; van Velzen et al, 2013), and the pharmacovigilance program for varicella vaccine in Europe and United States (Galea et al, 2008; Goulleret et al, 2010). However, unlike the study population with a grievous illness, these prior approaches were conducted in generally healthy populations. As an indicator of how well patients are reporting suspected herpetic infection, it is anticipated that study patients should report infection within the range of occurrence for the general population (ie, frequent recurrences of

oro-labial lesions are reported by 3% to 5% of the general population (Rooney et al, 1993).

### 8.9.2 External Validity of Study Design

Generalizability of study results may be limited by use of a study population based on a convenience (ie, not random) sample of study sites participating in the Postmarketing IMLYGIC Surveillance Program. Study sites that are selected will be among those with the earliest adoption of IMLYGIC. While the study patients will be recruited from these study sites, the patient inclusion and exclusion criteria are limited to best reflect any use of IMLYGIC in real-world, clinical practice. To describe if the Study 20130193 patients are representative of broader population of IMLYGIC patients, all patients in the screening log and the study patients will be reported by proportion for sex, age, and disease stage.

### 8.9.3 Withdrawal From Treatment, Procedures, and Study

**A p**atient has the right to withdraw fully from the study at any time and for any reason without prejudice to his or her future medical care by the physician or the institution. Withdrawal of full consent for a study means that the patient does not wish to or is unable to continue further study participation; patient data up to withdrawal of consent will be included in the patient's study data. Any patient may withdraw consent to participate in the study at any time during the study. The Investigator will discuss with the patient appropriate procedures for withdrawal from the study.

Should a patient request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable eCRF.

Reasons for removal from protocol-specified observation might include:

- withdrawal of consent
- death
- los**t** to follow-up.

## 9. PROTECTION OF PATIENTS

### 9.1 Informed Consent

Where an informed consent is required per local regulations, an initial sample ICF is provided for the Investigator or designee to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Clinical Study Manager to the

Investigator or designee. The written informed consent form is to be prepared in the language of the potential patient population.

Before a patient's participation in the study, the Investigator or designee will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study, and answer all questions regarding the study.

The acquisition of informed consent is to be documented in the patient's medical records, and the ICF is to be signed and personally dated by the patient or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed ICF must be provided to the patient or the patient's legally authorized representative.

If local regulations do not require an informed consent to be signed but mandate that the subject is notified about the study, the investigator or designee should document the notification process in the subject's medical record.

If a potential patient is illiterate or visually impaired, the Investigator must provide an impartial witness to read the ICF to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the ICF to attest that informed consent was freely given and understood.

### 9.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

A copy of the protocol, proposed ICF, other written patient information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF must be received by Amgen before study can be executed. The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The Investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures. The Investigator is responsible for obtaining annual IRB approval and IRB/IEC renewal throughout the duration of the study. Copies of the Investigator's reports, where applicable by local regulations and the IRB/IEC continuance of approval must be sent to Amgen.

Any protocol amendments will be submitted to the local IRB for their review and approval. Annual IRB approval/renewal throughout the duration of the study will be obtained and copies of the IRB continuance of approval will be sent to Amgen.

### 9.3 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained for documents submitted to Amgen.

- Patients are to be identified by a unique patient identification number. The key to re-identify patients must not be shared with Amgen.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the eCRFs demographics page, in addition to the unique patient identification number, include the age at the time of enrollment.
- For serious adverse events reported to Amgen, patients are to be identified by their unique patient identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not for submission to Amgen (eg, signed ICFs, as applicable) are to be kept in confidence by the Investigator, except as described below.

In compliance with local country regulations, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the patient's original medical records for verification of study-related activities and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study-related records, including personal information.

## 10. COLLECTION, RECORDING, AND REPORTING OF SAFETY INFORMATION AND PRODUCT COMPLAINTS

### 10.1 Definition of Reportable Events

#### 10.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated

with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease.
- Events associated with the discontinuation of the use of a product(s) (eg, appearance of new symptoms).

It is the Investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

### 10.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other medically important serious event" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a health care facility.

"Other medically important serious events" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

### 10.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) include:

- Medication errors, overdose/underdose, whether accidental or intentional, misuse, addiction, or abuse, involving an Amgen product,
- Use of an Amgen product while pregnant and/or breast feeding,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Accidental or Occupational exposure,

- Any lack or loss of intended effect of the product(s)

### 10.1.4 Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution to market or clinic. This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

Product complaints of IMLYGIC will be collected.

## 10.2 Safety Collection, Recording and Submission to Amgen Requirements

The Investigator is responsible for ensuring that safety events (adverse events, serious adverse events, product complaints, and other safety findings) observed by the Investigator or reported by the patient that occur after signing of the ICF through 30 days after the last dose of IMLYGIC; in addition, safety events (adverse events and serious adverse events) related to IMLYGIC treatment (as deemed by the Investigator) occurring 30 days after the last dose of IMLYGIC through 5 years of follow-up are recorded in the patient's appropriate study documentation. Those safety events which are considered serious must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator's awareness. Non-serious Adverse Events must be reported in an expeditious manner, not to exceed 15 calendar days of awareness.

Protocol Exempted Events

One of the objectives of the study is to monitor for long-term safety of IMLYGIC. Hence, adverse events and serious adverse events occurring 30 days after the last dose of IMLYGIC through 5 years after the first IMLYGIC dose and deemed related to IMLYGIC by the Investigator are monitored and reported during the long term follow-up as outlined in Section **10**.1. Adverse events and serious adverse events not deemed related to IMLYGIC by the investigator, and products complaints as defined in Section **10.**1.4, and other safety findings as defined in Section **10**.1.3 such as medication errors, overdose/underdose, misuse, addiction, abuse, off-label use involving IMLYGIC are not monitored during the long term follow-up because IMLYGIC is not administered to patients enrolled during the long-term follow-up phase of the study. Therefore, these other safety events are only monitored and reported during treatment with IMLYGIC and up to the safety visit (ie, up to 30 days after the last dose of IMLYGIC). The pregnancy

and lactation cases are monitored during treatment and through 3 months after the last dose of IMLYGIC.

If any of the exempted reportable events during the long-term follow-up have a fatal outcome, they should be considered a serious adverse event and must be collected and reported individually within 1 business day from when the Investigator first becomes aware of the event.

All safety information that is not specified in this section is to be collected and submitted to Amgen within the specified time frame.

Protocol-exempted events and reportable events that are suspected to be related to any Amgen medicinal product where there is no exposure to IMLYGIC should be spontaneously reported to Amgen within 1 business day of investigator/vendor awareness. A list of all Amgen medicinal products can be found in the following link: https://wwwext.amgen.com/amgen-worldwide

To spontaneously report a reportable event to Amgen, refer to the following link to locate your Local Amgen contact information by country: https://wwwext.amgen.com/contact-us/product-inquiries

Additional details on what to collect and report to Amgen for the reportable event can be found in the following link: https://wwwext.amgen.com/products/global-patient-safety/adverse-event-reporting

Reportable events suspected to be related to any non-Amgen medicinal product should be reported to the local authority in line with the local country requirements.

If the EDC system is unavailable to the site staff to report the adverse event, the information is to be reported to Amgen via a paper Adverse Event Contingency Report Form within 1 business day of the Investigator's awareness for serious adverse events and within 15 calendar days for non-serious adverse events. For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

See Appendix **B** for sample Safety Report Form(s) and Form for Postmarket Report of Suspected IMLYGIC Associated Adverse Event for HCP or Close Contact; Appendix **C** for Additional Safety Reporting Information regarding the adverse event grading scale used in this study; and Appendix **D** for sample Pregnancy and Lactation Notification Worksheets.

The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record.

Information provided about the event must be consistent with information recorded on study CRFs where safety data may also be recorded (eg, Event CRF).

### 10.2.1 Collection of Pregnancy and Lactation Information

**Female Subjects Who Become Pregnant**

Investigator will collect pregnancy information on any female subject who becomes pregnant following exposure to talimogene laherparepvec through 3 months after discontinuing talimogene laherparepvec.

Information will be recorded on the Pregnancy Notification Form (see Appendix **D**). The worksheet must be submitted to Amgen Safety within 1 business day of when investigator first becomes aware of the subject's pregnancy (Note: investigator is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide Investigator with a consent form and questionnaire to collect additional information. After obtaining the female subject's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant following exposure to talimogene laherparepvec through 3 months after discontinuing of the talimogene laherparepvec. This information will be forwarded to Amgen Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of pregnancy will be reported to Amgen Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is considered another safety finding, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.

If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the Investigator will report the event as a serious adverse event.

**Male Subjects with Partners who Become Pregnant [or Were Pregnant at the Time of Enrollment]**

In the event a male subject fathers a child following exposure to talimogene laherparepvec, and for an additional 3 months after discontinuing talimogene laherparepvec, the information will be recorded on the Pregnancy Notification Form. The form (see Appendix **D**) must be submitted to Amgen Safety within 1 business day of when the Investigator first becomes aware of the pregnancy. (Note: Investigator is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide Investigator with a consent form and questionnaire to collect additional information. The Investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

After obtaining the female partner's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Safety.

Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of the pregnancy will be reported to Amgen Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

**Collection of Lactation Information**

Investigator will collect lactation information on any female subject who breastfeeds while taking talimogene laherparepvec through 3 months after discontinuing talimogene laherparepvec.

Information will be recorded on the Lactation Notification Form (see Appendix **D**) and submitted to Amgen Safety within 1 business day of when the Investigator first becomes aware of the lactation exposure.

With the female subject's signed consent for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking

talimogene laherparepvec through 3 months after discontinuing talimogene laherparepvec.

### 10.2.2 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IRBs/IECs or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of reportable events in accordance with local procedures and statutes.

## 11. ADMINISTRATIVE AND LEGAL OBLIGATIONS

### 11.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC or other relevant ethical review board must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB/IEC or other relevant ethical review board to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IRB/IEC or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to Amgen.

## 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The protocol and an abstract of results will be posted as per guidelines for studies meeting the criteria for postauthorization safety studies.

Upon completion, the study will be submitted for peer-review publication.

### 12.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states the following:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the

version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.

- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

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## 14. APPENDICES

# Appendix A. ENCePP Checklist for Study Protocols



Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

## ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

**Study title:**
A post-marketing, prospective cohort study of patients treated with talimogene laherparepvec (Imlygic®) in clinical practice to characterize the risk of herpetic infection among patients, close contacts, and healthcare providers; and long-term safety in treated patients

**Study reference number:**
20130193

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | 16 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | 16 |
| 1.1.3 Study progress report(s) | ☒ | ☐ | ☐ | 16 |
| 1.1.4 Interim progress report(s) | ☒ | ☐ | ☐ | 16 |
| 1.1.5 Registration in the EU PAS register | ☒ | ☐ | ☐ | 1 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 16 |

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | | | | |
| 2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 17 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 19 |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 21 |
| 2.1.4 Which formal hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☐ | ☐ | ☒ | |

Comments:
This estimation study is not testing a hypothesis

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design) | ☒ | ☐ | ☐ | 20 |
| 3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated? | ☒ | ☐ | ☐ | 23 |
| 3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year) | ☒ | ☐ | ☐ | 25 |

Comments:

| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | 20 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period? | ☒ | ☐ | ☐ | 20 |
| 4.2.2 Age and sex? | ☒ | ☐ | ☐ | 21 |
| 4.2.3 Country of origin? | ☒ | ☐ | ☐ | 20 |
| 4.2.4 Disease/indication? | ☒ | ☐ | ☐ | 21 |
| 4.2.5 Co-morbidity? | ☒ | ☐ | ☐ | 21 |
| 4.2.6 Seasonality? | ☐ | ☐ | ☒ | |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 20 |

Comments:
Seasonality not relevant to cancer therapy

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure) | ☒ | ☐ | ☐ | 22 |

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study) | ☒ | ☐ | ☐ | 30 |
| 5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use) | ☒ | ☐ | ☐ | 22 |
| 5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☐ | ☒ | |
| 5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured? | ☐ | ☐ | ☒ | |

Comments:

Exposure is to a therapy and all subjects will have exposure.

| **Section 6: Endpoint definition and measurement** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 6.1 Does the protocol describe how the endpoints are defined and measured? | ☒ | ☐ | ☐ | 23 |
| 6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☒ | ☐ | ☐ | 25 |

Comments:

| **Section 7: Confounders and effect modifiers** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders) | ☐ | ☐ | ☒ | |
| 7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect) | ☐ | ☐ | ☒ | |

Comments:

This is a single arm study for estimation and no comparison groups.

| **Section 8: Data sources** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.) | ☒ | ☐ | ☐ | 21 |
| 8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.) | ☒ | ☐ | ☐ | 23 |
| 8.1.3 Covariates? | ☒ | ☐ | ☐ | 21 |
| 8.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☐ | ☐ | ☒ | |
| 8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event) | ☐ | ☐ | ☒ | |
| 8.2.3 Covariates? (e.g. age, sex, clinical and drug use | | | | |

| **Section 8: Data sources** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| history, co-morbidity, co-medications, life style, etc.) | ☐ | ☐ | ☒ | |
| 8.3 Is a coding system described for: | | | | |
| 8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10) | ☐ | ☐ | ☒ | |
| 8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events) | ☒ | ☐ | ☐ | 30 |
| 8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System) | ☐ | ☐ | ☒ | |
| 8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other) | ☒ | ☐ | ☐ | 22 |

Comments:

| **Section 9: Study size and power** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 9.1 Is sample size and/or statistical power calculated? | ☒ | ☐ | ☐ | 25 |

Comments:

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 10.1 Does the plan include measurement of excess risks? | ☐ | ☐ | ☒ | |
| 10.2 Is the choice of statistical techniques described? | ☒ | ☐ | ☐ | 28 |
| 10.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 28 |
| 10.4 Are stratified analyses included? | ☐ | ☐ | ☒ | |
| 10.5 Does the plan describe methods for adjusting for confounding? | ☐ | ☐ | ☒ | |
| 10.6 Does the plan describe methods addressing effect modification? | ☐ | ☐ | ☒ | |

Comments:
This is a single arm study for estimation and no comparison groups.

| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 11.1 Is information provided on the management of missing data? | ☒ | ☐ | ☐ | 26 |
| 11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 25 |
| 11.3 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 30 |
| 11.4 Does the protocol describe possible quality issues related to the data source(s)? | ☒ | ☐ | ☐ | 31 |
| 11.5 Is there a system in place for independent review of study results? | ☐ | ☐ | ☒ | |

Comments:

**ENCePP Checklist for Study Protocols (Revision 2)** 4

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss: | | | | |
| 12.1.1 Selection biases? | ☒ | ☐ | ☐ | 31 |
| 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods) | ☒ | ☐ | ☐ | 31 |
| 12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☒ | ☐ | ☐ | 25 |
| 12.3 Does the protocol address other limitations? | ☒ | ☐ | ☐ | 31 |

Comments:

| **Section 13: Ethical issues** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described? | ☒ | ☐ | ☐ | 33 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☒ | ☐ | ☐ | 33 |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 33 |

Comments:

| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document future amendments and deviations? | ☒ | ☐ | ☐ | 1 |

Comments:

| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g. to regulatory authorities)? | ☒ | ☐ | ☐ | 37 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 37 |

Comments:

Name of the main author of the protocol: _____

Date: 13/4/2016

Signature: _____

**ENCePP Checklist for Study Protocols (Revision 2)** 5

# Appendix B. Sample Safety Reporting Forms

## Completion Instructions - Electronic Adverse Event Contingency Report Form (For use for clinical trial studies using Electronic Data Capture [EDC])

**NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.**

**General Instructions**

**The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.**

**Types of Events to be reported on this form**

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   **Site Number*** – Enter your assigned site number for this study

   **Investigator*, Country*, Reporter*, Phone No., and Fax No.** – Enter information requested

2. **Subject Information**

   **Subject ID Number*** – Enter the entire number assigned to the subject

   **Age at event onset, Sex, and Race** – Enter the subject's demographic information

   **End of Study date** – If the subject has already completed the study or terminated the study early, enter the End of Study date

***If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.***

3. **Serious Adverse Event**

   **Provide the date the Investigator became aware of this Information**

   **Serious Adverse Event Diagnosis or Syndrome*** –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   **Date Started*** – Enter date the adverse event first started (not the date on which the event met serious criteria )rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   **Date Ended** – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   **If event occurred before the first dose of Investigational Product (IP)/drug under study**, add a check mark in the corresponding box.

   **Is event serious?* – Indicate Yes or No. This is a mandatory field.**

   **Serious Criteria Code* – This is a mandatory field for serious events.** Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   **Relationship to IP** – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   **Relationship to Amgen device*** – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   **Outcome of Event*** – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   **If event is related to a study procedure**, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event.

## Completion Instructions - Electronic Adverse Event Contingency Report Form (for use for Studies using Electronic Data Capture [EDC])

**Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.**

Protocol specified hospitalizations are exempt.

***At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.***

5. **IP Administration including Lot # and Serial # when known / available.**
   **Blinded or open-label** – If applicable, indicate whether the investigational product is blinded or open-label
   **Initial Start Date** – Enter date the product was first administered, regardless of dose.
   **Date of Dose Prior to or at the time of the Event** – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   **Dose, Route, and Frequency at or prior to the event** – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   **Action Taken with Product** – Enter the status of the product administration.
6. **Concomitant Medications**
   **Indicate if there are any medications.**
   **Medication Name, Start Date, Stop Date, Dose, Route, and Frequency** – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   **Co-suspect** – Indicate if the medication is co-suspect in the event
   **Continuing** – Indicate if the subject is still taking the medication
   **Event Treatment** – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   **Indicate if there are any relevant laboratory values.**
   **For each test type,** enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   **Indicate if there are any tests, including any diagnostics or procedures.**
   **For each test type,** enter the date, name, results and units (if applicable).

***At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.***

10. **Case Description**
    **Describe Event** – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

**Complete the signature section at the bottom of page 3 and fax the form to Amgen.** *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

| A<br>Study # 20130193<br>Talimogene<br>Laherparepvec<br>(TVEC) | **Electronic Serious Adverse Event Contingency Report Form**<br>**For Restricted Use** |
|---|---|

**Reason for reporting this event via fax**
**The Clinical Trial Database (eg. Rave):**

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

***<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>***

**1. SITE INFORMATION**

| Site Number | Investigator | Country |
|---|---|---|
| | | |

| Reporter | Phone Number | Fax Number |
|---|---|---|
| | ( ) | ( ) |

**2. SUBJECT INFORMATION**

| Subject ID Number | Age at event onset | Sex | Race | If applicable, provide End of Study date |
|---|---|---|---|---|
| | | ☐F ☐M | | |

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day ____ Month _____ Year _____

**3. SERIOUS ADVERSE EVENT**

**Provide the date the Investigator became aware of this information: Day_____ Month____ Year_____**

| Serious Adverse Event diagnosis or syndrome<br>If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report<br>*List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.* | Date Started<br>Day Month Year | Date Ended<br>Day Month Year | Check only if event occurred before first dose of IP | Is event serious? | If serious, enter Serious Criteria code (see codes below) | Relationship<br>Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? | | | | | | Outcome of Event<br>1-Resolved<br>2-Not resolved<br>3-Fatal<br>4-Unknown | Check only if event is related to study procedure<br>eg, biopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | TVEC | | 1-Device | | 2-Device | | 3-Device | | | |
| | | | | | | No-✓ | Yes-✓ | No-✓ | Yes-✓ | No-✓ | Yes-✓ | No-✓ | Yes-✓ | | |
| | | | | ☐Yes ☐No | | | | | | | | | | | |
| | | | | ☐Yes ☐No | | | | | | | | | | | |
| | | | | ☐Yes ☐No | | | | | | | | | | | |

**Serious Criteria:** **01** Fatal; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

**4. Was subject hospitalized or was a hospitalization prolonged due this event?** ☐No ☐Yes If yes, please complete all of Section 4

| Date Admitted<br>Day Month Year | Date Discharged<br>Day Month Year |
|---|---|
| | |

**5. Was IP/drug under study administered/taken prior to this event?** ☐No ☐Yes If yes, please complete all of Section 5

| | | Date of Initial Dose<br>Day Month Year | Prior to, or at time of Event<br>Date of Dose<br>Day Month Year | Dose | Route | Frequency | Action Taken with Product<br>01 Still being Administered<br>02 Permanently discontinued<br>03 Withheld | Lot # and Serial # |
|---|---|---|---|---|---|---|---|---|
| IP/Amgen Device: | | | | | | | | |
| TVEC | ☐ blinded ☒ open label | | | | | | | Lot # _____<br>☐ Unknown<br>Serial # _____<br>☐ Unavailable / Unknown |

| A<br>Study # 20130193<br>Talimogene<br>Laherparepvec<br>(TVEC) | Electronic Serious Adverse Event Contingency Report Form<br>For Restricted Use |
|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| <<IP/Device>> | ☐ blinded ☐ open label | | | | | | | Lot # _____<br>☐ Unknown<br>Serial #<br>_____<br>☐ Unavailable / Unknown |

| Site Number | Subject ID Number |
|---|---|
| | |

**6. CONCOMITANT MEDICATIONS (eg, chemotherapy)** Any Medications? ☐ No ☐ Yes If yes, please complete:

| Medication Name(s) | Start Date (Day Month Year) | Stop Date (Day Month Year) | Co-suspect No✓ | Co-suspect Yes✓ | Continuing No✓ | Continuing Yes✓ | Dose | Route | Freq. | Treatment Med No✓ | Treatment Med Yes✓ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

**7. RELEVANT MEDICAL HISTORY** ***(include dates, allergies and any relevant prior therapy)***

**8. RELEVANT LABORATORY VALUES** ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

| Test / Unit / Date (Day Month Year) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

**9. OTHER RELEVANT TESTS** ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

| Date (Day Month Year) | Additional Tests | Results | Units |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

| A<br>Study # 20130193<br>Talimogene<br>Laherparepvec<br>(TVEC) | Electronic Serious Adverse Event Contingency Report Form<br>For Restricted Use |
|---|---|

| Site Number | Subject ID Number |
|---|---|
| | |

**10. CASE DESCRIPTION** ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

| | | |
|---|---|---|
| Signature of Investigator or Designee -<br>_____<br>*I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.* | Title | Date |

| AMGEN Study # 20130193 | **Postmarket Report of Suspected IMLYGIC® Associated Adverse Event for Health Care Provider or Close Contact**<br>***Notify Amgen within one business day of awareness*** | ❑New<br>❑Follow-up |
|---|---|---|

*SELECT OR TYPE IN A FAX#*

**SITE INFORMATION** (if associated patient is in a postmarket study)

| Site Number | Investigator | Country |
|---|---|---|
| | | |

| Reporter | Phone Number ( ) | Fax Number ( ) |
|---|---|---|
| | | |

**INFORMATION FOR THE PERSON EXPERIENCING EVENT**

| Event ID | Associated Patient ID or Patient initials | Age at Time of Event | Gender | If female, is she currently pregnant? |
|---|---|---|---|---|
| - | | _____ years | ☐ Male ☐ Female | ☐ Declined to provide ☐ No<br>☐ Yes (date of LMP)<br>__ __ / __ __ / __ __ __ __ (dd/mm/yyyy) |

Indicate the relationship of the person experiencing the event with the associated (treated) patient:

| ☐ Health care professional | ☐ Close contact who is: | ☐ Residing with treated patient<br>☐ Providing medical assistance/care to patient<br>☐ Regularly in close contact with treated patient<br>☐ Other (specify) _____ |
|---|---|---|

**1. IMLYGIC® (talimogene laherparepvec) administration to the treated patient (if known)**

a. Date of the first dose administration
☐ __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

b. Date of the last dose administration
☐ __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)
☐ Not applicable (eg, exposure occurred during administration preparation)
Product Lot Number: _____ or Unknown (✔):_____

**2. History of a person experiencing event**

a. Previous history of herpetic infections
☐ No
☐ Yes: Date of last episode __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

b. If the answer to a. above is YES, please complete:

| Signs/symptoms of herpetic infections prior to known or suspected exposure to IMLYGIC | Present? | How many times per year? |
|---|---|---|
| ☐ Oral herpes (cold sores/fever blister) ☐ Genital herpes (blister lesions in genital area) | | |
| Other suspected symptoms (describe): _____ | | |

c. Has the person ever been treated with antivirals, eg, acyclovir, for herpetic infection?
☐ No ☐ Not sure ☐ Yes (Date): __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)
Method of treatment administration: ☐ Topical ☐ Oral ☐ Intravenous

d. Was the person taking any medications (other than antivirals addressed in 2c above) at the time of the event?
☐ No ☐ Not sure ☐ Yes (Provide details below)

| Medication | Indication | Start Date (dd/mm/yyyy) | Dose/Frequency | Continuing? If no, stop date (dd/mm/yyyy) |
|---|---|---|---|---|
| | | ___/___/_____ | | ☐ Yes ☐ No ___/___/_____ |
| | | ___/___/_____ | | ☐ Yes ☐ No ___/___/_____ |

| AMGEN Study # 20130193 | **Postmarket Report of Suspected IMLYGIC® Associated Adverse Event for Health Care Provider or Close Contact**<br>***Notify Amgen within one business day of awareness*** | ❑New<br>❑Follow-up |
|---|---|---|

**3. Details of each known or suspected exposure prior to this event**

| Exposure Information | Check all boxes that apply to known exposure(s) | |
|---|---|---|
| | **Physical Direct Contact With Treated Patient** | **Caregiver** |
| Date and Exposure ID<br>____/____/_____<br>dd mm yyyy<br>Exposure ID:<br>____-____<br>☐ Date and Exposure ID not known | ☐ Sleep together<br>☐ Touched lesion facing side of dressing<br>☐ Touched injected lesion directly<br>☐ Intimate physical contact (kissing, sexual intercourse)<br>☐ Other (describe below): | ☐ Touched lesion facing side of dressing<br>☐ Touched injected lesion directly<br>☐ Needle stick<br>☐ Splash back/Direct contact of IMLYGIC with unprotected skin/mucosa<br>☐ Other (describe below): |
| Date and Exposure ID<br>____/____/_____<br>dd mm yyyy<br>Exposure ID:<br>____-____<br>☐ Date and Exposure ID not known | ☐ Sleep together<br>☐ Intimate physical contact (kissing, sexual intercourse)<br>☐ Touched lesion facing side of dressing<br>☐ Touched injected lesion directly<br>☐ Other (describe below): | ☐ Touched lesion facing side of dressing<br>☐ Touched injected lesion directly<br>☐ Needle stick<br>☐ Splash back/Direct contact of IMLYGIC with unprotected skin/mucosa<br>☐ Other (describe below): |
| Date and Exposure ID<br>____/____/_____<br>dd mm yyyy<br>Exposure ID:<br>____-____<br>☐ Date and Exposure ID not known | ☐ Sleep together<br>☐ Intimate physical contact (kissing, sexual intercourse)<br>☐ Touched lesion facing side of dressing<br>☐ Touched injected lesion directly<br>☐ Other (describe below): | ☐ Touched lesion facing side of dressing<br>☐ Touched injected lesion directly<br>☐ Needle stick<br>☐ Splash back/Direct contact of IMLYGIC with unprotected skin/mucosa<br>☐ Other (describe below): |

**4. Evaluations, Diagnosis and Laboratory Measures**

| Diagnostic | Results/Units | Reference Range/Units | Date (dd/mm/yyyy) |
|---|---|---|---|
| Live virus assay | | | ___/___/_____ |
| Real-time polymerase chain reaction (qPCR) | | | ___/___/_____ |
| Serologic test (antibody test) | | | ___/___/_____ |
| Other (specify): | | | ___/___/_____ |
| Other (specify): | | | ___/___/_____ |

**Talimogene laherparepvec qPCR swab done?** ☐ **Yes:** **If yes**, provide date(s) lesion(s) was/were swabbed:_____

_____

☐ **No:** **If no**, indicate reason why swab was not done ☐ Declined to consent ☐ Other (please specify):

_____

_____

 

| AMGEN Study # 20130193 | **Postmarket Report of Suspected IMLYGIC® Associated Adverse Event for Health Care Provider or Close Contact**<br>***Notify Amgen within one business day of awareness*** | ❑New<br>❑Follow-up |
|---|---|---|

**5. Adverse Event Information:**

a. Complete **each** row below for a person experiencing herpetic signs and symptoms since the associated patient began treatment with IMLYGIC. *Populate each row of the following table:*

| **Signs or Symptoms** | **Present?** | **Location on body** | **If Serious, enter Serious Criteria code** *(see codes below)* | **Relationship to IMLYGIC** | **Date started** dd/mm/yyyy | **Date ended** dd/mm/yyyy |
|---|---|---|---|---|---|---|
| Oral herpes (cold sores/fever blister, eg, on face, mouth, lip or nose single or multiple red papular or ulcerated lesions at mucocutaneous junction, around mouth or on face, with pain, tingling or itching | ☐ Yes ☐ No | | | ☐ Yes ☐ No ☐ Unknown | ___/___/___ | ___/___/___ |
| Herpetic whitlow (painful, itchy blister lesion on fingertips of hand) | ☐ Yes ☐ No | | | ☐ Yes ☐ No ☐ Unknown | ___/___/___ | ___/___/___ |
| Genital herpes (blister lesions in genital area) | ☐ Yes ☐ No | | | ☐ Yes ☐ No ☐ Unknown | ___/___/___ | ___/___/___ |
| Herpetic keratitis - eye signs and/or symptoms (redness, pain, photophobia [intolerance to light], blurred vision, tearing) | ☐ Yes ☐ No | | | ☐ Yes ☐ No ☐ Unknown | ___/___/___ | ___/___/___ |
| Herpetic encephalitis - neurological signs and/or symptoms (eg, fever associated with headache, vomiting, lethargy, psychiatric symptoms, seizures, weakness, confusion, or memory loss) | ☐ Yes ☐ No | | | ☐ Yes ☐ No ☐ Unknown | ___/___/___ | ___/___/___ |
| Skin lesion/rash | ☐ Yes ☐ No | | | ☐ Yes ☐ No ☐ Unknown | ___/___/___ | ___/___/___ |
| Other signs/symptoms: (DESCRIBE) | ☐ Yes ☐ No | | | ☐ Yes ☐ No ☐ Unknown | ___/___/___ | ___/___/___ |

| **Serious Criteria:** | 01 Fatal 02 Immediately life-threatening 03 Required hospitalization 04 Prolonged hospitalization<br>05 Persistent or significant disability/incapacity 06 Congenital anomaly/birth defect 07 Other significant medical hazard |
|---|---|

**b. Provide, if available, final diagnosis or syndrome:**

_____

_____

| AMGEN Study # 20130193 | **Postmarket Report of Suspected IMLYGIC® Associated Adverse Event for Health Care Provider or Close Contact**<br>***Notify Amgen within one business day of awareness*** | ❑New<br>❑Follow-up |
|---|---|---|

**6. Action Taken:**

a. Did either of the following occur since the associated patient began treatment with IMLYGIC?

☐ Hospitalization ☐ No ☐ Yes: Date of hospitalization __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

☐ Consultation with other healthcare provider(s) ☐ No ☐ Yes: Date of consult(s)

Provide available hospitalization and consult reports with this document. Conceal personal identifiers and write the assigned Event ID number on reports.

__ __ / __ __ / __ __ __ __ (dd/mm/yyyy)
__ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

b. Did the exposed/potentially exposed person receive treatment with antivirals, eg, acyclovir, for herpetic infection?
☐ No ☐ Not sure ☐ Yes (Date): __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

Method of treatment administration: ☐ Topical ☐ Oral ☐ Intravenous

c. Did the person receive any other treatment?
☐ No ☐ Not sure ☐ Yes (Provide details below)

| Medication | Indication | Start Date (dd/mm/yyyy) | Dose/Frequency | Continuing? If no, stop date (dd/mm/yyyy) |
|---|---|---|---|---|
| | | ___/___/_____ | | ☐ Yes ☐ No ___/___/_____ |
| | | ___/___/_____ | | ☐ Yes ☐ No ___/___/_____ |

d. Chronological summary of symptoms (narrative of events):

| Signature of Investigator or Designee | Title | Date of report |
|---|---|---|
| | | |

## Appendix C. Additional Safety Reporting Information

Adverse Event Severity Scoring System

For oncology studies, the CTCAE is to be used. The Common Terminology Criteria for Adverse Events (CTCAE) is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

## Appendix D. Pregnancy and Lactation Notification Forms



AMGEN® Pregnancy Notification Form

**Report to Amgen at:** USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

### 1. Case Administrative Information

**Protocol/Study Number:** 20130193

**Study Design:** ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

### 2. Contact Information

**Investigator Name** _____ **Site #** _____

**Phone** (____)_____ **Fax** ( ___ )_____ **Email** _____

**Institution** _____

**Address** _____

### 3. Subject Information

**Subject ID #** _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):**____(in years)

### 4. Amgen Product Exposure

| Amgen Product | Dose at time of conception | Frequency | Route | Start Date |
|---|---|---|---|---|
| | | | | mm____/dd____/yyyy____ |

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

### 5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐Yes ☐No ☐Unknown ☐N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

**Print Name:** _____ **Title:** _____

**Signature:** _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Amgen Proprietary - Confidential

## AMGEN® Lactation Notification Form

**Report to Amgen at:** USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

### 1. Case Administrative Information

**Protocol/Study Number:** 20130193

**Study Design:** ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

### 2. Contact Information

**Investigator Name** _____ **Site #** _____

**Phone** (_____)_____ **Fax** (_____)_____ **Email** _____

**Institution** _____

**Address** _____

### 3. Subject Information

**Subject ID #** _____ **Subject age (at onset):**____(in years)

### 4. Amgen Product Exposure

| Amgen Product | Dose at time of breast feeding | Frequency | Route | Start Date |
|---|---|---|---|---|
| | | | | mm_____/dd_____/yyyy_____ |

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

### 5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐Yes ☐No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

**Print Name:** _____ **Title:** _____

**Signature:** _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

## Appendix E. Sample Laboratory Report from Viracor

Viracor-IBT LABORATORIES

LABORATORY REPORT

**Subject Number, Initials, MISC:** VALIDATION, ADULT S
**SUBJ MISC:**TEST
**Site Number:**
**Visit #:**
**Viracor-IBT Patient ID:** PPD
**ORDER MISC 2:**
**Report Delivered:**PPD

**Client Accession ID:**
**Patient Sex:**PPD
**ORDER MISC 1:**
**ORDER MISC 3:**
**Received:**PPD

**CLIENT:**
Viracor-IBT Validation
123 Main
Suite B
Anywhere, Mo 11223

**RESULTS**

*T-VEC qPCR (lesion swab) TV00*
Viracor-IBT Accession ID: PPD
Client Accession ID:
Collected:PPD
Final - Approved PPD
Performed at: Viracor-IBT Laboratories - 1001 NW Technology Dr., Lee's Summit, MO | CLIA# 26D-0983643

| TEST | RESULT | UNIT |
|---|---|---|
| T-VEC qPCR | Not Detected | copies/ug |

Dear Healthcare Provider,

Please find enclosed the results of the quantitative polymerase chain reaction (qPCR) laboratory test for talimogene laherparepvec DNA in swab from lesion of suspected herpetic origin.

Thank you for making this sample available for testing. The enclosed test results should be used in conjunction with clinical findings, and should not be the sole basis for a diagnosis or treatment decision.

The information from this testing will also add to the overall safety profile of this biopharmaceutical product. If you require further information about this product, please contact Amgen Medical Information at 1-800-772-6436 if you are located in the USA. If you are located outside USA, call the Amgen Medical Information office in your country or region, using the contact details provided in your Amgen qPCR test information pack. If you do not have the contact information, please call +1-805-447-1000, or "Submit an Inquiry" at http://www.amgenmedinfo.com/Home.

The 50% detection cut off for this qPCR assay is 7.46 copies/ug and the limit of quantitation (LOQ) is 18.0 copies/ug. T-VEC DNA detected between the cut off and LOQ will be reported as Detected BQL.

This test was developed and its performance characteristics determined by Viracor-IBT Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. Results should be used in conjunction with clinical findings, and should not form the sole basis for a diagnosis or treatment decision.