Summary Table of Study Protocol

Title	A Cross-sectional Survey to Evaluate Patient Knowledge of Safety Messages Included in the Patient Safety Brochure and Patient Alert Card for IMLYGIC®
Protocol version identifier	Superseding Amendment **3, version 1.0**
Date of last version of the protocol	**17 July 2019**
EU Post Authorization Study (PAS) Register No	**EUPAS31213**
Active Substance	Talimogene Laherparepvec (T-VEC)
Medicinal Product	IMLYGIC®
Product Reference	EMEA/H/C/002771
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	The purpose of this study is to evaluate patients' awareness of the IMLYGIC Patient Safety Brochure and Patient Alert Card, and knowledge of the key messages included in the IMLYGIC Patient Safety Brochure among patients who received IMLYGIC. Primary The primary objective of this study is to evaluate patients' knowledge levels of the key messages included in the IMLYGIC Patient Safety Brochure among patients who receive IMLYGIC. Secondary The secondary objective of this study is to evaluate patients' levels of receipt, reading, and use of the IMLYGIC Patient Safety Brochure and Patient Alert Card among patients who receive IMLYGIC.
Country(ies) of Study	Germany, the Netherlands

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Investigator's Agreement

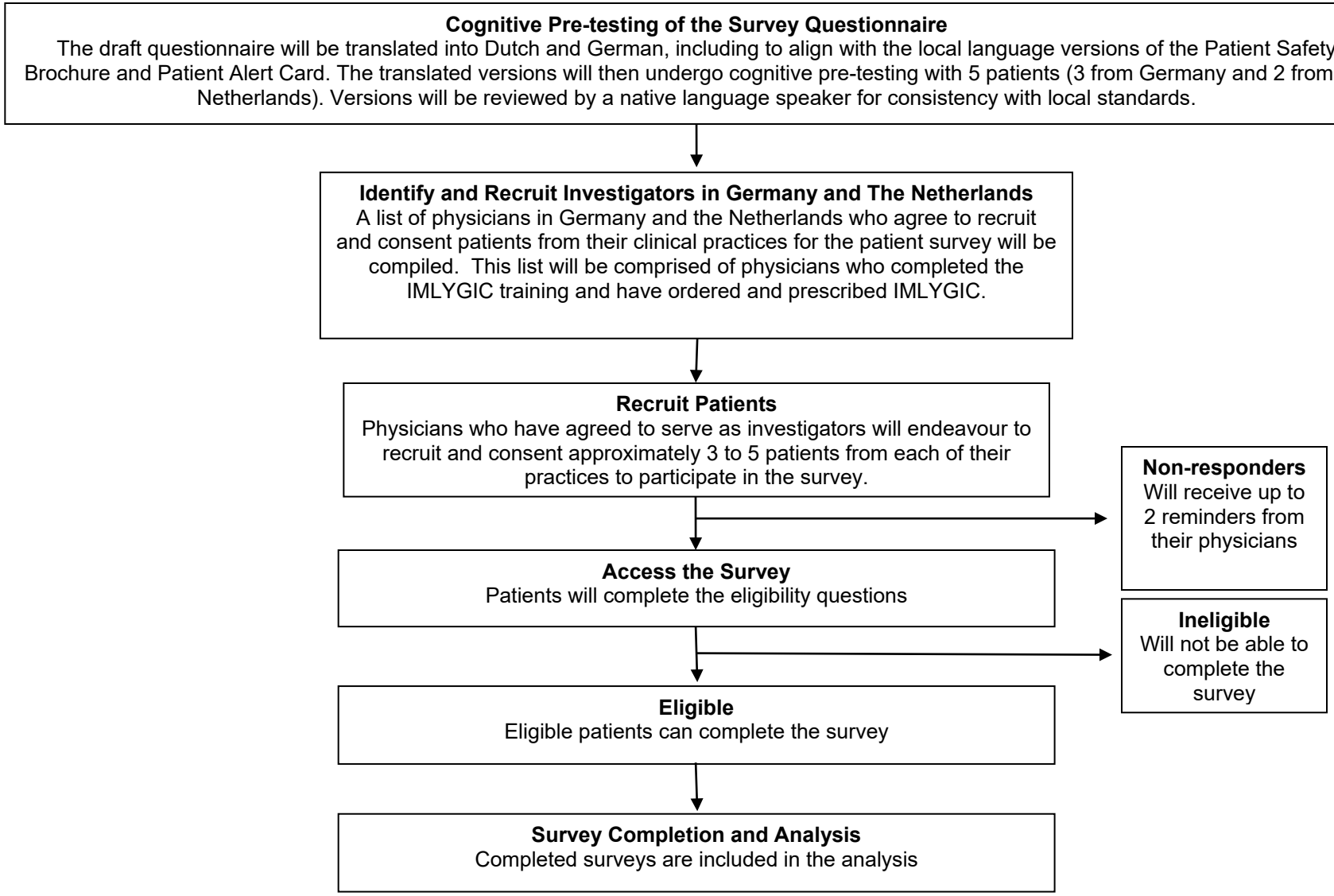
I have read the attached protocol entitled A Cross-sectional Survey to Evaluate Patient Knowledge of Safety Messages Included in the Patient Safety Brochure and Patient Alert Card for IMLYGIC, dated **14 October** 2019, and agree to abide by all provisions set forth therein.

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 Date (DD Month YYYY)

Study Design Schema



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2. List of Abbreviations

Abbreviation	Description
ADR(s)	adverse drug reaction(s)
AE	adverse event
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DRR	durable response rate
EDC	electronic data capture
EMA	European Medicines Agency
FMV	fair market value
GM-CSF	granulocyte macrophage colony-stimulating factor
GVP	Good Pharmacovigilance Practice
HCP	healthcare professional
HSV-1	herpes virus type 1
ICF	informed consent form
IEC	independent ethics committee
PASS	post-authorisation safety study
PIL	patient information leaflet
RMM(s)	risk minimisation measure(s)
RMP	risk management plan
SAP	statistical analysis plan
SOP	standard operating procedure
SQETCF	Site Qualification and Education & Training Confirmation Form (SQETCF)
UK	United Kingdom

3. Responsible Parties

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4. Abstract

- **Study Title**

  A Cross-sectional Survey to Evaluate Patient Knowledge of Safety Messages Included in the Patient Safety Brochure and Patient Alert Card for IMLYGIC®

- **Study Background and Rationale**

  An estimated 100,000 new cases of melanoma were diagnosed and over 22,000 deaths occurred in Europe in 2012. The age-standardised incidence rate of melanoma is estimated to be approximately 11 per 100,000 in Europe, however, incidence rates vary widely across Europe. In Europe, the 5-year survival rate is on average 83%, however, survival decreases with more advanced stage of disease and varies widely.

  Since 2011 the treatment landscape for patients with advanced melanoma has changed rapidly to include immunotherapy such as checkpoint inhibitors, targeted agents (eg, BRAF and MEK inhibitors), and oncolytic immunotherapy. Oncolytic viruses are a new treatment modality in melanoma. Talimogene laherparepvec (IMLYGIC®) is a herpes simplex virus type-1-derived oncolytic immunotherapy designed to selectively replicate within tumours and produce granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance systemic antitumour immune responses. In the open-label phase III trial (OPTiM), IMLYGIC showed an increase in durable response rate (DRR) compared to GM-CSF treatment, with a DRR of 25.2% compared to 1.2%, respectively, in patients with unresectable regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) melanoma who had no bone, brain, lung, or other visceral disease. Based on the positive OPTiM trial results, the European Medicines Agency (EMA) approved IMLYGIC on 17 December 2015. IMLYGIC is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung, or other visceral disease. IMLYGIC is the first oncolytic viral drug to treat unresectable and metastatic melanoma. IMLYGIC is directly injected into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance.

Due to its viral nature, IMLYGIC presents potential risks of primary herpetic infection during treatment and/or reactivation from latent state after treatment. In addition, IMLYGIC presents potential risks of stimulation or reactivation of latent wild-type Herpes Simplex Virus Type 1 (HSV-1) in patients. Furthermore, secondary transmission and infection by IMLYGIC can occur among patients' close contacts and healthcare providers (HCPs). Herpetic infection can present clinically as oral or genital herpes, herpetic whitlow, or herpetic gladiatorum of the skin, herpetic keratitis, herpetic conjunctivitis, herpetic uveitis, herpetic encephalitis, and disseminated herpetic infection. To ensure safe administration and handling, IMLYGIC was authorised with additional risk minimisation measures (RMMs) in Europe. These additional RMMs include a controlled distribution programme, educational material targeted for both HCPs and patients, with the primary aim to inform HCPs and patients and their close contacts about the potential risks associated with IMLYGIC.

For patients, the primary additional RMMs are the Patient Safety Brochure and Patient Alert Card. In accordance with European pharmacovigilance legislation introduced in 2012 and Good Pharmacovigilance Practice (GVP), the effectiveness of additional RMM should be evaluated. This survey is classified as a post-authorisation safety study (PASS, category 3) and this study will be designed and conducted in accordance with GVP Modules VIII and XVI.

- **Research Question and Objective(s)**

  Primary Objective(s)

  The primary objective is to evaluate patients' knowledge levels of the key messages included in the IMLYGIC Patient Safety Brochure among patients who receive IMLYGIC, specifically:

  - The risk of disseminated herpetic infection, which can be life-threatening, in immunocompromised individuals.
  - The risk of spread of the IMLYGIC virus to patients' close contacts if they have direct contact with the patient's body fluids or injection sites. Advice given is to avoid such contact, to tell close contacts to avoid such contact, and that in case of accidental exposure to clean the affected area with soap and water or a disinfectant.
  - The risk of symptomatic herpes infection during or after treatment with IMLYGIC. Information is given on the signs and symptoms of herpes infection, the need for patients and their close contacts to tell their doctor right away if any of these signs and symptoms are present, and that a herpetic-type lesion can be tested to see if it is caused by IMLYGIC.
  - The instruction on keeping injection sites covered at all times with airtight and watertight dressings at all times. Advice is given on how to apply the dressing, and to replace the dressing immediately if it becomes loose or falls off, and to tell close contacts to wear gloves if helping to change dressings.
  - The instruction to avoid touching or scratching the injection sites.
  - That the use of IMLYGIC during pregnancy may harm the patient's unborn baby and to tell their doctor if the patient becomes pregnant or plans to become pregnant.

- The instructions to minimise the risk of exposure of blood and body fluids to close contacts for the duration of IMLYGIC treatment through 30 days after the last administration of IMLYGIC, including a list of activities to avoid (eg, shared used of toothbrushes or razor blades).
- The instructions for disposal of used dressings and cleaning materials.

Secondary Objective(s)

- To evaluate patients' levels of receipt and reading of the IMLYGIC Patient Safety Brochure and receipt, reading, knowing the purpose of, and use (ie, carrying) of the Patient Alert Card among patients who receive IMLYGIC.

Exploratory Objective(s)

- An exploratory objective is a composite variable on patients' knowledge levels for all 8 primary endpoints.

- **Study Design/Type**

  This is a multi-national, non-interventional, cross-sectional survey study.

- **Study Population**

  The target population is patients who receive IMLYGIC in Germany and the Netherlands. A list of HCPs in Germany and the Netherlands who agree to recruit and consent patients from their clinical practices to participate in the patient survey will be compiled from lists of HCPs who have previously completed the IMLYGIC training and have ordered and prescribed IMLYGIC. HCPs who agree to serve as investigators will endeavour to recruit and consent approximately 3 to 5 patients from each of their practices to participate in the survey

- **Summary of Patient Eligibility Criteria**

  Inclusion criteria

  - Age ≥ 18 years old
  - Has received IMLYGIC at least once in the 3 months prior to completing the survey
  - Provides written informed consent, including permission to share their responses in aggregate with the EMA or national competent authorities, if requested
  - Able to read and understand in native language of each of the participating countries

  Exclusion criteria

  - Has participated in the cognitive pre-testing of the survey questionnaire to be used for this study
  - Current participation in an IMLYGIC clinical trial or expanded access programme
  - Has been a direct employee of Amgen, ICON, or the EMA within the year prior to completing the survey

- **Variables**
  - *Outcome Variable(s)*
    - Primary: Percentages of patients with correct responses to the knowledge-related questions. Success criteria for the primary endpoint percentages are at least 60% of patients provide a correct response to each individual knowledge-related question that has a minimum n = 30.
    - Secondary: Levels of awareness (receipt) and reading of the IMLYGIC Patient Safety Brochure and receipt, reading, knowing the purpose of, and use of the Patient Alert Card. Assessed as the percentages of patients who report receipt/reading/use.
    - Exploratory: a composite variable on the level of patients' knowledge for all primary endpoints; specifically, the distribution of percentages of patients who provide correct responses to all 8 of the knowledge-related questions
  - *Covariate(s)*
    - Patient characteristics
- **Study Sample Size**

  A sample of 30 to 50 completed patient surveys is targeted for this study. This sample size is determined based on both practical and statistical considerations.

  The primary evaluation criteria are the levels of patients' knowledge of the key messages included in the IMLYGIC patient-directed RMMs. A sample size of 50 respondents allows estimation of a minimum knowledge level of at least 60% with a precision of 14.2%.
- **Data Analysis**

  The primary analysis population will include all patients who have completed at least 1 of the endpoint questions in the survey. Frequencies, percentages, and corresponding 95% confidence intervals (CIs) will be used to summarise the endpoints for the primary analysis set overall, by country, and by subgroups. For each knowledge level question, the percentage of patients who answer each question correctly will be estimated and assessed against the 60% (± 95% CI) target. For secondary endpoints, percentages and 95% CI will be estimated.

  The primary analysis will be performed by having read vs. not read the IMLYGIC Patient Safety Brochure. An analysis to evaluate the impact of recall bias will be performed by repeating the primary analysis stratified by tertiles of time since patients first received IMLYGIC to when they completed the survey.

5. Amendments and Updates

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason
1	11 April 2019	See summary of changes		
2	17 July 2019	See summary of changes		
3	**14 October 2019**	**See summary of changes**		

6. Milestones

Milestone	Planned date
Cognitive pre-test complete	18 February 2020
Start of data collection	29 April 2020
End of data collection	27 October 2020
Final report of study results	17 February 2021

* These timelines are subject to receiving timely approvals from national competent authorities and ethics committees which may vary by country.

7. Rationale and Background

An estimated 100,000 new cases of melanoma were diagnosed and over 22,000 deaths occurred in Europe in 2012 (Ferlay *et al*, 2013). At a time when the incidence of some of the more common cancers has declined (such as lung cancer), the incidence of melanoma has increased consistently in Europe (eg, in the United Kingdom [UK], the age-standardised incidence rate of malignant melanoma increased by 278% between 1993 and 2014, though the projected rate of increase in incidence is likely to slow in future years) (Smittenaar *et al*, 2016). The age-standardised incidence rate of melanoma is estimated to be approximately 11 per 100,000 in Europe. However, incidence rates have varied widely across Europe, ranging between 1.3 per 100,000 population in Albania to 25.8 per 100,000 population in Switzerland (Ferlay *et al*, 2013).

Detected early stage melanoma is associated with high patient survival rates, however, if attempted excision of the lesion is unsuccessful, there is a high likelihood of recurrence, with 75% recurring within 2 years and 95% within 5 years after initial diagnosis (Brantsch *et al*, 2008).

Although metastatic risk is low in most patients, approximately 85% of metastases involve regional lymph nodes, followed by distant metastasis in the skin, lung, liver, bone, and brain. The risk of locoregional recurrence or distant metastasis is dependent on the pathological tumour characteristics, such as tumour location (ear, lips, areas of chronic ulcers or inflammation), clinical size of lesion (> 2 cm in diameter), histological depth extension (beyond the subcutaneous tissue), histological type, and degree of differentiation, recurrence, and immunosuppression (Stratigos *et al*, 2015).

In Europe, the 5-year survival rate is on average 83% (Crocetti *et al*, 2015). However, survival decreases with worsening stage and varies widely. Five-year survival is estimated to be > 95% for Stage 1, 65-93% for Stage II, 41-71% for Stage III, and 9-28% for Stage IV (Svedman *et al*, 2016). The 5-year recurrence free survival is estimated to be between 28% to 44% for Stage III.

7.1 Disease and Therapeutic Area

Since 2011 the treatment landscape for patients with unresectable or metastatic melanoma has changed rapidly to include immunotherapy (checkpoint inhibitors eg, anti-CTLA-4 [ipilimumab], anti-PD-1 [nivolumab, pembrolizumab]), targeted agents (BRAF and MEK inhibitors), and oncolytic viral therapy.

Systemic immunotherapies work to stimulate an individual's immune system to destroy cancer cells more effectively. Ipilimumab (Yervoy®), nivolumab (Opdivo®), and pembrolizumab (Keytruda®) are approved systemic therapies for unresectable and metastatic melanoma.

About 40-50% of melanomas have *BRAF* gene mutations and the majority of these mutations are *BRAF*^{V600E} (80-90%) or *BRAF*^{V600K} (10-20%). Melanoma patients with these *BRAF* mutations can be treated with *BRAF and MEK* targeted therapies. Approved targeted therapies include vemurafenib (Zelboraf®), dabrafenib (Tafinlar®), trametinib (Mekinist®), or a combination of dabrafenib plus trametinib.

Oncolytic viruses are another new treatment modality in melanoma. Talimogene laherparepvec (IMLYGIC®) is a herpes simplex virus type-1 genetically engineered to selectively replicate in, and kill, cancer cells without injuring normal tissues. IMLYGIC was approved as the first oncolytic immunotherapy to treat unresectable and metastatic melanoma.

7.1.1 Talimogene Laherparepvec (IMLYGIC)

Talimogene laherparepvec or IMLYGIC is a herpes simplex virus type-1-derived oncolytic immunotherapy designed to selectively replicate within tumours and produce granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance systemic antitumour immune responses. IMLYGIC is directly injected into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance (Harrington *et al*, 2017; Summary of Product Characteristics, 2018).

In the open-label phase III trial (OPTiM), the efficacy of IMLYGIC was compared with subcutaneously administered GM-CSF in patients with unresectable Stage IIIB/C and IV melanoma (Andtbacka *et al*, 2015). Countries participating in the OPTiM trial included Canada, South Africa, United States, and the UK. IMLYGIC showed an increase in durable response rate (DRR) compared to GM-CSF treatment, with a DRR of 25.2% compared to 1.2%, respectively, in patients with unresectable regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) melanoma who had no bone, brain, lung, or other visceral disease (Andtbacka *et al*, 2015; Harrington *et al*, 2016).

Based on the positive OPTiM trial results, the European Medicines Agency (EMA) approved IMLYGIC on 17 December 2015 (EMA, 2015). IMLYGIC is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung, or other visceral disease.

Due to its viral nature, IMLYGIC presents potential risks of primary herpetic infection during treatment, and reactivation from latent state after treatment. In addition, IMLYGIC presents potential risks of stimulation or reactivation of latent wild-type HSV-1 in patients and secondary transmission and infection by IMLYGIC among patients' close contacts and healthcare providers (HCPs). Herpetic infection can present clinically as oral or genital herpes, herpetic whitlow or herpetic gladiatorum of the skin, herpetic keratitis, herpetic conjunctivitis, herpetic uveitis, herpetic encephalitis, and disseminated herpetic infection.

7.1.1.1 Additional Risk Minimisation Measures (RMMs)

To inform safe and effective use, IMLYGIC was authorised with additional risk minimisation measures (RMMs) in Europe. These additional RMMs include a controlled distribution programme, educational material targeted for both HCPs and patients, with the primary aim to inform HCPs and patients about potential risks associated with IMLYGIC.

7.1.1.1.1 Controlled Distribution Programme

The controlled distribution programme for IMLYGIC manages the product supply chain to ensure that cold storage requirements are observed and to control the distribution of IMLYGIC to qualified centres and to patients.

The controlled distribution programme is in place to ensure that the following requirements are fulfilled before IMLYGIC is dispensed:

- Experienced HCPs are adequately trained in order to minimise the risk of occurrence of specified adverse drug reactions (ADRs) in patients, HCPs, and close contacts of the patients,
- HCPs and support personnel (eg, pharmacists) are trained regarding safe and appropriate storage, handling, and administration of IMLYGIC, and clinical follow-up for patients treated with IMLYGIC,
- HCPs and support personnel are provided with safety information (Patient Safety Brochure and Patient Alert Card) to communicate with patients and their family and caregivers, and
- Trained HCPs will record batch number information in patients' charts and on patients' alert card for all injections and to provide the batch number when reporting ADRs.

In Europe, IMLYGIC has a controlled distribution programme and physicians need to complete required training delivered by Amgen medical liaisons before they are authorised to receive shipments of IMLYGIC. Hospital sites with resources and facilities who can satisfactorily handle and administer IMLYGIC are eligible for training and qualification. Mandatory participants of the training include 1 experienced physician in the treatment of melanoma and 1 pharmacist primarily responsible for handling IMLYGIC. Optional participants in the training can include nurses, other physicians potentially treating patients with IMLYGIC, another pharmacist, or other pharmacy staff handling IMLYGIC at the site. Upon completion of training, sites are provided with IMLYGIC RMMs (eg, Patient Safety Brochures and Patient Alert Cards). Training is also documented via a Site Qualification and Education & Training Confirmation Form (SQETCF). Sites with evidence of SQETCF on file are authorised to be supplied with IMLYGIC.

7.1.1.1.2 Patient Safety Brochure

For patients, the primary additional RMM is the Patient Safety Brochure, which provides safety information for patients, including information patients can share with family, caregivers, and close contacts, on the following:

- The risk of disseminated herpetic infection, which can be life-threatening, in immunocompromised individuals.
- The risk of spread of the IMLYGIC virus to patients' close contacts if they have direct contact with the patient's body fluids or injection sites. Advice given is to avoid such contact, to tell close contacts to avoid such contact, and that in case of accidental exposure to clean the affected area with soap and water or a disinfectant.
- The risk of symptomatic herpes infection during or after treatment with IMLYGIC. Information is given on the signs and symptoms of herpes infection and the need for patients and their close contacts to tell their doctor right away if any of these signs and symptoms are present.
- The instruction on keep injection sites covered at all times with airtight and watertight dressings at all times. Advice is given on how to apply the dressing, and to replace the dressing immediately if it becomes loose or falls off, and to tell close contacts to wear gloves if helping to change dressings.
- Then instruction to avoid touching or scratching the injection sites.
- That the use of IMLYGIC during pregnancy may harm the patient's unborn baby and to tell their doctor if the patient becomes pregnant or plans to become pregnant.
- The instructions to minimise the risk of exposure of blood and body fluids to close contacts for the duration of IMLYGIC treatment through 30 days after the last administration of IMLYGIC, including a list of activities to avoid (eg, shared used of toothbrushes or razor blades).
- The instructions for disposal of used dressings and cleaning materials.

In addition to the Patient Safety Brochure, there is a Patient Alert Card for IMLYGIC. The Patient Alert Card is to be carried by the patient and presented to HCPs upon consultation or hospitalisation and informs the HCP that the patient has been treated with IMLYGIC and when the doses have been administered. The Patient Alert Card refers to the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) and provides contact details for further information. The Patient Alert Card also instructs patients and their close contacts to contact the listed doctor if they develop a herpetic lesion to be tested and if applicable, treated.

7.2 Rationale

In accordance with European pharmacovigilance legislation introduced in 2012 and Good Pharmacovigilance Practice (GVP) (European Commission, 2010), the effectiveness of additional RMM described in the Risk Management Plan (RMP) should be evaluated. The purpose of this survey study is to measure the effectiveness of the additional RMM for IMLYGIC. Specifically, the objectives are to measure knowledge and understanding of the information in the patient-directed additional RMM for IMLYGIC. This survey is classified as a post-authorisation safety study (PASS, category 3) and this study will be designed and conducted in accordance with GVP Modules VIII and XVI (European Medicines Agency, 2017a; European Medicines Agency, 2017b).

The proposed study utilises a cross-sectional survey study design. In Europe, Module XVI of GVP, selection of tools and effectiveness indicators of RMMs, references the use of “scientifically rigorous survey methods” to assess the awareness of the target audience and the level of knowledge achieved by educational interventions and/or information provision (European Medicines Agency, 2017a).

Health literacy can be a potential confounder for knowledge levels of the information conveyed in the patient-directed additional RMM. Specifically, knowledge levels measured in this study to evaluate the effectiveness of the additional RMM may be lowered due to health literacy. To assess the impact of health literacy on outcomes measured in this study, a brief health literacy questionnaire is included in the survey questionnaire (Chew et al, 2004).

7.3 Statistical Inference (Estimation or Hypothesis[es])

This study is a survey to estimate patients’ knowledge levels of the information included in the IMLYGIC RMMs. The results will therefore be descriptive in nature and no formal hypothesis will be tested.

8. Research Question and Objectives

The overall objective of this study is to evaluate patients' awareness of the IMLYGIC Patient Safety Brochure and Patient Alert Card and knowledge of the key messages included in the IMLYGIC Patient Safety Brochure among patients who receive IMLYGIC.

8.1 Primary

The primary objective of this study is to evaluate patients' knowledge levels of the key messages included in the IMLYGIC Patient Safety Brochure among patients who receive IMLYGIC, specifically:

- The risk of disseminated herpetic infection, which can be life-threatening, in immunocompromised individuals.
- The risk of spread of the IMLYGIC virus to patients' close contacts if they have direct contact with the patient's body fluids or injection sites. Advice given is to avoid such contact, to tell close contacts to avoid such contact, and that in case of accidental exposure to clean the affected area with soap and water or a disinfectant.
- The risk of symptomatic herpes infection during or after treatment with IMLYGIC. Information is given on the signs and symptoms of herpes infection, the need for patients and their close contacts to tell their doctor right away if any of these signs and symptoms are present, and that a herpetic-type lesion can be tested to see if it is caused by IMLYGIC.
- The instruction on keeping injection sites covered at all times with airtight and watertight dressings at all times. Advice is given on how to apply the dressing, and to replace the dressing immediately if it becomes loose or falls off, and to tell close contacts to wear gloves if helping to change dressings.
- The instruction to avoid touching or scratching the injection sites.
- That the use of IMLYGIC during pregnancy may harm the patient's unborn baby and to tell their doctor if the patient becomes pregnant or plans to become pregnant.
- The instructions to minimise the risk of exposure of blood and body fluids to close contacts for the duration of IMLYGIC treatment through 30 days after the last administration of IMLYGIC, including a list of activities to avoid (eg, shared used of toothbrushes or razor blades).
- The instructions for disposal of used dressings and cleaning materials.

8.2 Secondary

The secondary objective of this study is to evaluate patients' levels of receipt and reading of the IMLYGIC Patient Safety Brochure and receipt, reading, and use (**ie**, carrying) of the Patient Alert Card among patients who receive IMLYGIC. Patients' understanding of the purpose of the Patient Alert Card will also be assessed.

8.3 Exploratory

An exploratory objective is a composite variable on patients' knowledge levels for all 8 primary endpoints.

9. Research Methods

9.1 Study Design

This is a multi-national, non-interventional, cross-sectional survey study to evaluate the effectiveness of the patient-directed additional RMMs for IMLYGIC; specifically, the Patient Safety Brochure and Patient Alert Card. The survey will be conducted in a single wave in Germany and the Netherlands among patients that receive IMLYGIC. The target number of completed surveys is approximately 30 to 50, with ideally at least 15 completed surveys per participating country.

A convenience sample of patients will be recruited by HCPs who have agreed to recruit and consent patients to participate in this study; these HCPs will have already completed the training required for HCPs as part of the IMLYGIC controlled distribution programme and will have prescribed IMLYGIC to at least 3 patients. To facilitate patient recruitment, HCPs will be provided with survey information packs that contain all information and documents necessary for patients to participate in the survey. For interested participants who did not complete the questionnaire (ie, non-responders), up to two reminders will be given by their HCPs.

Data will be collected by on-line electronic data capture (EDC) or on paper, based on patient preference. Information collected will include the receipt and reading of the IMLYGIC Patient Safety Brochure and Patient Alert Card, knowledge of the key messages included in the IMLYGIC Patient Safety Brochure, and brief patient characteristics.

Prior to conducting the actual survey, the draft survey questionnaire will undergo cognitive pre-testing. The goals of cognitive pre-testing are to identify any survey questions that require clarification or revision based on areas of confusion revealed by patients in the cognitive pre-test interviews, and to ensure that translated versions of the questionnaire are conceptually and cross-culturally equivalent in each of the local country languages to avoid misunderstanding.

9.2 Setting and Study Population

The target population is patients who receive IMLYGIC in Germany and the Netherlands. These countries were selected as they have the largest use of IMLYGIC in Europe.

Approximately 12 sites will participate in Germany and the Netherlands. A list of HCPs who have completed the IMLYGIC controlled distribution programme training and have ordered and prescribed IMLYGIC will be approached about study participation. Those who agree to recruit and consent patients from their clinical practices to participate in the patient survey will serve as investigators and will endeavour to recruit and consent approximately 3 to 5 patients.

9.2.1 Study Period

The minimum planned period for data collection is 6 months.

As this is a single wave cross-sectional design, data from patients will be collected at 1 point in time.

9.2.2 Patient Eligibility

To determine patients' eligibility, screening questions will be administered prior to potential participants beginning the survey.

9.2.2.1 Inclusion Criteria

- Age ≥ 18 years old.
- Has received IMLYGIC at least once in the 3 months prior to completing the survey.
- Provides written informed consent, including permission to share their responses in aggregate with the EMA or national competent authorities, if requested.
- Able to read and understand in native language of each of the participating countries.

9.2.2.2 Exclusion Criteria

- Participated in the cognitive pre-testing of the survey questionnaire to be used for this study.
- Current participation in an IMLYGIC clinical trial or expanded access programme.
- Have been direct employees of Amgen, ICON, or the EMA within the year prior to completing the survey.

9.2.3 Matching

Not applicable.

9.2.4 Baseline Period

Not applicable. This is a cross-sectional study.

9.2.5 Study Follow-up

Not applicable. This is a cross-sectional study.

9.3 Variables

The survey questionnaire includes the following:

- Survey introduction that describes the survey objective and logistics.
- Screening questions to determine eligibility for survey participation.
- Questions regarding the receipt, reading, knowing the purpose of, and use of the IMLYGIC Patient Safety Brochure and Patient Alert Card.
- Questions to assess knowledge of the key messages included in the IMLYGIC Patient Safety Brochure, specifically:
    - The risk of disseminated herpetic infection, which can be life-threatening, in immunocompromised individuals.
    - The risk of spread of the IMLYGIC virus to patients' close contacts if they have direct contact with the patient's body fluids or injection sites. Advice given is to avoid such contact, to tell close contacts to avoid such contact, and that in case of accidental exposure to clean the affected area with soap and water or a disinfectant.
    - The risk of symptomatic herpes infection during or after treatment with IMLYGIC. Information is given on the signs and symptoms of herpes infection, the need for patients and their close contacts to tell their doctor right away if any of these signs and symptoms are present, and that a herpetic-type lesion can be tested to see if it is caused by IMLYGIC.
    - The instruction on keep injection sites covered at all times with airtight and watertight dressings at all times. Advice is given on how to apply the dressing, and to replace the dressing immediately if it becomes loose or falls off, and to tell close contacts to wear gloves if helping to change dressings.
    - Then instruction to avoid touching or scratching the injection sites.
    - That the use of IMLYGIC during pregnancy may harm the patient's unborn baby and to tell their doctor if the patient becomes pregnant or plans to become pregnant.
    - The instructions to minimise the risk of exposure of blood and body fluids to close contacts for the duration of IMLYGIC treatment through 30 days after the last administration of IMLYGIC, including a list of activities to avoid (eg, shared used of toothbrushes or razor blades).
    - The instructions for disposal of used dressings and cleaning materials.
    - Instruction to carry Patient Alert Card with them at all times.
- Brief questions on patients' characteristics and health literacy.

Survey question types are multiple choice, yes/no, and true/false questions with no free text allowed.

9.3.1 Exposure Assessment

No tests or reference treatments are utilised in this cross-sectional, non-interventional survey of patients.

9.3.2 Outcome Assessment

Measures of success

The results of the study will be interpreted considering an acceptable level of knowledge and awareness. The study estimates and associated 95% confidence intervals (CIs) will be calculated. The selection of a threshold for success is subjective and not based on a priori knowledge, experience, or established scientific criteria in the education or risk communication or evaluation literature. Therefore, the results will be contextualised with other available information.

Primary endpoints

The primary endpoints are the percentages of patients with correct responses to the knowledge-related questions (Section 8.1).

Success criteria for the primary endpoint percentages are at least 60% of patients provide a correct response to each individual knowledge-related question that has a minimum n = 30.

Secondary endpoints

The secondary endpoints are the percentages of patients that report receiving, reading, and using the IMLYGIC Patient Safety Brochure and Patient Alert Card.

Exploratory endpoints

- An exploratory endpoint is a composite variable on the level of patients' knowledge across all knowledge-related questions; specifically, the distribution of percentages of patients who provide correct responses to all 8 of the knowledge-related questions.

9.3.3 Covariate Assessment

The following sociodemographic characteristics will be collected and used to describe the sample:

- Country
- Age group (< 65 vs. ≥ 65 years)
- Gender
- Highest level of education attained (primary school, secondary school, university degree or higher)
- Health literacy
- Length of time received IMLYGIC
- Current vs. past use of IMLYGIC

9.3.4 Validity and Reliability

The survey questionnaire will undergo cognitive pre-testing with 5 patients (3 from Germany and 2 from the Netherlands) prior to conducting the actual survey in Germany and the Netherlands. This sample size is based on both qualitative research standards and feasibility considerations. In qualitative research, a sample of 12 interviews for homogeneous groups is considered to be sufficient to achieve saturation (saturation is the point in the data collection process where no new relevant information is elicited from individual interviews) (Guest *et al*., 2006). From a feasibility perspective, based on the limited use of IMLYGIC, it would be impractical to conduct pre-testing with 12 patients. The goal of cognitive pre-testing is to identify any survey questions that require clarification or revision based on areas of confusion or miscomprehension revealed by patients in the cognitive pre-test interviews.

Pre-testing will be completed through one-on-one interviews. To be eligible to participate in the cognitive pre-test, patients must have received IMLYGIC within the last 3 months. Patients will be recruited by HCPs managing care for them, using a targeted list of HCPs who agree to recruit patients for the pre-testing provided by Amgen. Due to an anticipated time commitment of 45 to 60 minutes to participate in the cognitive pre-test, patients who complete the cognitive pre-test will receive fair market value (FMV) compensation if allowed per the local law and regulations.

During the conduct of the cognitive pre-test, the survey questionnaire will be presented item by item, and feedback will be obtained for each question. The interviewer will also record information regarding any questions received from patients or other feedback indicating difficulty with any question or wording.

The questionnaire will be developed in British English, however, since the study is only being conducted in Germany and the Netherlands, translations will be obtained first, and then cognitive pre-testing will be conducted using the Dutch and Germany questionnaire translations. As part of the translations, each questionnaire will be further reviewed to align with the local language IMLYGIC Patient Safety Brochure and Patient Alert Card approved for each participating country, and for consistency in use of local patient terminology.

9.4 Data Sources

Data will be collected by on-line EDC or on paper based on patient preference.

A convenience sample of patients will be recruited from the target population of patients who received IMLYGIC from HCPs who have agreed to recruit and consent patients for

this study. The HCPs will have previously completed the required training for HCPs as part of the IMLYGIC controlled distribution programme and will have prescribed IMLYGIC to at least 3 patients. To facilitate patient recruitment, HCPs will be provided with survey information packs that include an invitation letter, study information sheet or informed consent form, a paper survey and pre-addressed/postage paid envelope for returning the completed paper survey to ICON, and information on how to access the on-line survey should a patient prefer to complete the on-line version. To preserve patient confidentiality, the materials in each survey information pack will be labelled with a unique identifier. HCPs will be instructed to record which unique identifier was assigned to each patient so that when HCPs are provided with information on which unique identifiers for their sites have been received, HCPs will be able to track which patients have already completed a survey vs. need to be reminded to complete a survey. The unique identifier will also facilitate HCP FMV payments based on the number of completed surveys received from their sites.

The survey is anticipated to be conducted in a minimum period of 6 months. For sites which take longer to complete required regulatory notifications and approvals, this period may be extended. Depending on response rates, follow-up reminders will be sent to HCPs who are recruiting and consenting patients for participation in the patient survey. Metrics on survey participation will be tracked to monitor progress and to issue follow-up reminders to sites if less than the target number of completed surveys has been received. The maximum number of follow-up attempts per site will not exceed two.

9.5 Study Size

A sample of 30 to 50 completed patient surveys is targeted for this study. This sample size is determined based on both practical and statistical considerations, including the low use of IMLYGIC in Europe, the shortened survival of patients with late stage melanoma, and the low response rate for surveys in general. Although all efforts will be made to reach the target, the actual sample size will depend on patients' availability and willingness to participate in the survey.

The primary evaluation criteria are the levels of patients' knowledge of the key messages included in the IMLYGIC Patient Safety Brochure and Patient Alert Card. As such, the study sample size has been based on the primary endpoint. Table 1 provides the precision and two-sided 95% confidence interval (CI) around expected knowledge levels by various numbers of completed surveys for this study. A sample size of 50 patient respondents allows estimation of a patient knowledge level of at least 60% with a precision of 14.2% (Table 1).

Table 1. Precision and 95% Confidence Intervals for Various Combinations of Sample Size and Knowledge Rates

Sample Size	Probable Rates of Respondent Knowledge							
	60%		70%		80%		90%	
	Precision (%)	95% CI	Precision (%)	95% CI	Precision (%)	95% CI	Precision (%)	95% CI
20	22.4	36.1-80.9	21.2	45.7-88.1	19.0	56.3-94.3	15.2	68.3-98.8
30	18.3	40.6-77.3	17.3	50.6-85.3	15.4	61.4-92.3	12.2	73.5-97.9
40	15.9	43.3-75.1	15.0	53.5-83.4	13.2	64.4-90.9	10.5	76.3-97.2
50	14.2	45.2-73.6	13.3	55.4-82.1	11.9	66.3-90.0	9.2	78.2-96.7

Note: Calculated using PASS 13 software, * confidence intervals for 1 proportion, simple asymptotic formula (Hintze J, 2014).

9.6 Data Management

Survey data collection will be completed in a suitable software platform for the creation and delivery of surveys. Surveys completed on paper will be entered by ICON into the same platform used for surveys completed on-line. Data collected will be stored at secure servers and will be maintained to ensure compliance with applicable local or national regulations.

Response sets for all multiple-choice questions will be randomised to minimise bias. To minimise likelihood that respondents would look up answers and/or discuss the survey while taking it, respondents will be asked to complete the survey in 1 sitting and will not be allowed to revise their answers after they advance to the next question.

Survey database lock is anticipated to occur shortly after the survey is closed. To reduce opportunity for bias, survey respondents will not be contacted to clarify or revise their responses.

Additional details regarding data collection, management of missing data, data storage, and validation procedures will be detailed in the survey manual and statistical analysis plan (SAP).

Data management will be in accordance with the standard operating procedures (SOPs) of ICON.

9.6.1 Obtaining Data Files

Not applicable. This study involves primary data collection and will not use data from existing databases.

9.6.2 Linking Data Files

Not applicable. This study involves primary data collection and will not use data from existing databases; therefore, no linkage is required.

9.6.3 Review and Verification of Data Quality

This study will evaluate patients' knowledge of safety messages included in the Patient Safety Brochure and Patient Alert Card for IMLYGIC. To reduce opportunity for bias, survey respondents will not be contacted to clarify or revise their responses.

9.7 Data Analysis

Statistical analyses will be descriptive. A SAP will be developed and will describe all planned analyses in detail, along with any specifications for tables, listings, and figures to be produced. All analyses will be performed using appropriate statistical software (**eg,** SAS® Version 9.0 or later). A report summarising the results of the survey will be developed.

9.7.1 Planned Analyses

9.7.1.1 Primary Analysis

The primary analysis will be performed at a single time point after the survey database has been closed.

The primary analysis population will include all patients who have completed at least 1 of the primary or secondary endpoint questions in the survey (questions 1-15). Denominators used to calculate knowledge levels for individual survey questions will reflect the number of respondents who completed each individual survey question including responses of 'don't know/not sure'.

The primary criteria are knowledge levels of the key messages conveyed in the IMLYGIC Patient Safety Brochure (Section 9.3). Success criteria for the primary criteria is defined as at least 60% of patients provide a correct response to each individual knowledge-related question (questions 1-6 and 8-10).

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

Descriptive data analyses will be conducted. Descriptive statistics for continuous data will include N, means, and standard deviations. Results for some continuous variables may include ranges (minimums and maximums) and medians as well. Categorical data will be summarised using frequency counts and percentages. Levels of receipt, reading, use, and knowledge will be calculated with 95% 2-sided CI and will be reported overall and by country.

Data analysis will be performed by ICON in accordance with ICON's SOPs for statistical programming.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Missing data will be reviewed solely for the purposes of deriving the endpoints. No replacement or imputation will be performed. Descriptive statistics for continuous variables will include the available n, and descriptive statistics for categorical variables will include a category for "I don't know" and "missing", when applicable.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrollment

The following variables will be described, overall and by country:

- Survey status
  - Number and percentage of surveys with eligibility questions completed
  - Number and percentage of surveys with all, and partial, completion of the primary and secondary effectiveness endpoint questions
- Eligibility (Yes/No)
  - If No, reasons for exclusion (ie, number and percentage of patients who do not meet each specific eligibility criteria)
  - Primary analysis set (number and percentage of patients in the primary analysis set)

9.7.2.3.2 Description of Patient Characteristics

Frequencies and percentages will be used to summarise the distribution of patients' characteristics, including missing responses, for the primary analysis set overall, and by country.

9.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

Frequencies, percentages, and corresponding 95% CIs will be used to summarise the primary and secondary endpoints for the primary analysis set overall, by country, and by subgroups. For each knowledge-related question, the percentage patients who answer each question correctly will be estimated and assessed against the 60% (± 95% CI) target.

Frequencies and percentages will be used to summarise the distribution of all response choices, including missing responses, for all single questions regarding receipt, reading, use, and knowledge of the information included in the IMLYGIC Patient Safety Brochure and Patient Alert Card. This will be performed for the primary analysis set overall and by country.

9.7.2.5 Sensitivity Analysis

9.7.2.5.1 Subgroup Analysis

All analyses will be performed overall and by country.

In addition, the primary analysis will be performed overall, and also stratified by the following subgroups, if there are at least 10 patients in each applicable subgroup: age group (in tertiles or quartiles based on the distribution of the final data), gender, highest educational level attained, and length of time received IMLYGIC.

9.7.2.5.2 Other Sensitivity Analysis

The primary analysis will be performed by having read (all or some) vs. not read (no or don't know/not sure) the IMLYGIC Patient Safety Brochure. An analysis to evaluate the impact of recall bias will be performed by repeating the primary analysis stratified by tertiles of time since patients first received IMLYGIC to when they completed the survey.

9.8 Quality Control

SOPs will be followed where appropriate to ensure data quality and integrity, including archival of statistical programs, documentation of data cleaning, and validation of derived variables and analyses.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

This study will evaluate patients' knowledge of safety messages included in the Patient Safety Brochure and Patient Alert Card for IMLYGIC. However, information included in these materials is also available from other sources such as the IMLYGIC PIL. Therefore, it may not be possible to attribute the study results solely to the effectiveness of the Patient Safety Brochure and Patient Alert Card.

Recall bias is an inherent limitation when assessing knowledge levels, especially if there is a long lag time between exposure to educational material and assessment of knowledge. The impact of recall bias will be assessed by evaluating the time since patients first received IMLYGIC to when they completed the survey.

Measures to minimise information bias for this study are:

- Response sets for all multiple-choice questions are randomised,
- Patients are instructed to complete the survey in one sitting (to minimise the likelihood of looking up the correct answers),
- Questions must be answered in sequence (skipping ahead is not permitted),

- Responses cannot be changed once submitted (going back to change previously answered questions is not permitted), and
- Patients who complete a survey will not be contacted to clarify or revise their survey responses.

9.9.2 External Validity of Study Design

A primary limitation of a cross-sectional survey is selection bias due to the use of a convenience sample and/or low response rates. The impact of selection bias can be minimised through robust outreach to recruit a representative sample of patients who receive IMLYGIC in Europe. HCPs from the two countries with the largest use of IMLYGIC in Europe (Germany and the Netherlands) will be recruited to serve as study investigators to minimise selection bias for this survey. These HCPs will be asked to invite all appropriate patients from their practices to participate in the survey.

Generalisability of the study results may be limited in that the study population is based on a convenience sample. To promote generalisability, HCPs will be requested to invite all eligible patients from their practices to participate in the survey. It is possible that patients who accept to participate in the survey may be different from those who do not participate. Patient characteristics will be compared to other populations in other real-world studies of IMLYGIC that are published.

9.9.3 Analysis Limitations

This study will endeavour to collect 30 to 50 completed patient surveys. From a statistical perspective, this sample size is small, and therefore, estimates of knowledge levels may lack precision.

10. Protection of Human Subjects

10.1 Informed Consent

In accordance with local regulations and the ethical principles that have their origin in the principles of the Declaration of Helsinki, investigators must ensure that patients are clearly and fully informed about the purpose of the study, potential risks, and their rights and responsibilities when participating in this study. Patient informed consent to participate in this survey will be obtained prior to completing the survey questionnaire. By signing the Informed Consent Form (ICF), the patient consents to participate in the survey.

10.2 Institutional Review Board/Independent Ethics Committee

This type of study requires review and approval by an Independent Ethics Committee (IEC) in Germany and the Netherlands and an ICF from the patients for their

participation in the survey. Thus, the study will be conducted under the auspices of an IEC (central or local as applicable) in each country, as defined in local regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

10.3 Patient Confidentiality

To maintain confidentiality, a unique numeric code will be assigned to each patient. This unique code will be entered in the study-specific survey database and only the investigator will have access to the link between the patient's unique code and their identity.

All personal data will be treated in compliance with the General Data Protection Regulation and all applicable local laws and regulations.

10.4 Subjects Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate steps for withdrawal of their consent from the study.

11. Collection, Recording, and Reporting of Safety Information and Product Complaints

This study is collecting information from patients via a survey conducted at a single timepoint to assess patients' knowledge of information included in the IMLYGIC Patient Safety Brochure and Patient Alert Card. The survey does not involve collection of any patient-specific clinical outcomes nor does it include questions intended to identify safety events (adverse events, product complaints, and other safety findings). However, it is possible that during their participation in the survey, a patient may report a safety event (**eg**, in an open text field in the on-line survey questionnaire or in the margin of a paper survey questionnaire).

11.1 Definition of Safety Events

11.1.1 Adverse Events

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

An adverse event can therefore be any unfavourable 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.

11.1.2 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 subject 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 healthcare 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 subject 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.

11.1.3 Other Safety Findings

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

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse involving an Amgen product,
- Pregnancy and lactation exposure,
- Transmission of infectious agents,

- Reports of uses outside the terms for authorized use of the product including off-label use,
- Occupational exposure,
- Any lack or loss of intended effect of the product(s).

11.1.4 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 product after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

- Talimogene Laherparepvec

11.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from patients using questionnaires at a single time point. All safety events (adverse events, product complaints, and other safety findings) considered to have occurred following subject exposure to IMLYGIC will be collected if reported at the time of the survey. The Investigator is responsible for ensuring that all safety events they become aware of during study period, are recorded in the subject's appropriate study documentation. Those safety events which are considered serious must also be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of ICON's awareness. Non-serious Adverse Events (AEs) must be reported in an expeditious manner, not to exceed 15 calendars days of ICON's awareness.

11.2.1 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 serious adverse events in accordance with local procedures and statutes.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, competent authority notifications must be completed where applicable per local governing law and/or regulations. The independent ethics committee (IEC) must be informed of all amendments and give approval, if applicable. The Investigator **must** send a copy of the approval letter from the IEC 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 IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. 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 PASS. The results of this study are to be submitted for publication.

13.1 Publication Policy

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

1. 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.

14. Compensation

Not applicable.

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16. Appendices

Appendix A. List of Stand-alone Documents

No.	Title
1	*Questionnaire for Patients who Receive IMLYGIC*

Appendix B. ENCePP Checklist for Study Protocols

20180062 ENCePP
Checklist for Study Pr

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 section number 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). 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 Cross-sectional Survey to Evaluate Patient Knowledge of Safety Messages Included in the Patient Safety Brochure and Patient Alert Card for IMLYGIC™

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	

[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.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.1, 11.2

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2, 9.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.1
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	9.1, 9.2
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Duration of follow-up?	☐	☐	☒	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.4

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.4
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.1, 8.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.4
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.2 Does the protocol address:	☒	☐	☐	9.9
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	9.3.3

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2, 9.4
9.1.3 Covariates?	☒	☐	☐	9.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2, 9.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3.
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7.2.5.1
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2.2
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.2, 9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.3

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13

Comments:

Name of the main author of the protocol: PPD [redacted] PhD, MPH

Date: 20/August/2018

Signature: PPD [redacted]

Appendix C. Sample Safety Reporting Form(s)

20180062. Safety reporting form.pdf

Observational Research Safety Reporting Form Instructions

This form is for use for observational studies that are using paper report form

General Instructions

The protocol will provide instruction on what types of events to report for the study. *Indicates a mandatory field.

What to report on this form:

- **All adverse events (AEs) are associated with the Amgen drug irrespective of causal relationship of the event to the study drug or seriousness, unless instructed differently by the protocol.**
- **The following safety findings are to be reported on this form as events regardless of association with an AE:**
  - **medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving the Amgen product**
  - **transmission of infectious agents**
  - **reports of uses outside the terms for authorized use of the product including off label use**
  - **occupational exposure**
  - **any lack or loss of intended effect of the product(s)**
  - **product complaint (PC)**
  - **adverse device effect (ADE)**

The following should not be reported on this form and should be reported via the normal process set up for the study

- **pregnancy and lactation reports**

1. **Initial or Follow-up*** – Please tick the appropriate box
2. **Site Number* –** Enter your assigned site number for this study. **Subject Number* –** Enter the entire number assigned to the subject.
3. **Indicate event type* –** Tick the relevant box which applies to the event(s) you are reporting. Please note, more than one box can be ticked.
4. **Contact Details* –** Provide your name, phone, address, etc. (These contact details should be for the Vendor or Investigator)
5. **Reporter ID* –** Provide name or ID of reporter, phone, address, etc. (This could be the Investigator details if vendor details are added in section 4.
6. **HCP Contact Details (if other than reporter)* –** Provide name or ID of reporter, country, phone, address, etc.
7. **Patient* –** Enter the subjects demographic information.
8. **Medical History (include primary diagnosis)* –** 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.
9. **Suspect Product Information (include dosing details)* –** Provide Product/Device information, Indication, start date, stop date, dose, route, frequency, Lot#, Serial#. It is important that all efforts are taken to provide the Lot number, were possible.
10. **AE, Other Safety Finding, PC/ADE Information*:**

    AE 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.

    Onset Date* – Enter date the AE first started rather than the date of diagnosis or hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

    Resolved Date* – Enter date the AE ended. For serious events, this is 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.

    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 AE. Protocol specified hospitalizations are exempt.

    Serious Criteria Code* – This is a mandatory field for serious events. Select the appropriate code for the event(s) being reported

    Action Taken* – State what action has been taken with suspect drug/device.

    Outcome* – Enter the code for the outcome of the event at the time the form is completed if outcome is known.

    Severity* – State the severity of the safety event being reported.

Relationship to Product/Device*:

Relationship to Amgen drug under study* – The Investigator must determine and enter the relationship of the event to the Amgen drug under study at the time the event is initially reported.

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)**

11. **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.

12. **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.

13. **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).

14. **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 each page and fax the form to Amgen.

Project ID: 20180062	AMGEN	**Observational Research Safety Reporting Form**	**Date of Reporter Awareness:**
			Date Reported to Amgen:
	Fax reports to: Amgen Local Office	*<<populate LAO fax here or delete language>>*	

1. Initial: ☐ **Follow-up:** ☐

2. Site Number: **Subject Number:**

3. Indicate event type: ***(Please tick all that apply)*** ☐ **AE/Other Safety Finding** ☐ **Product Complaint (PC)** ☐ **Adverse Device Effect (ADE)**

4. Contact Details (Vendor/Investigator)

Name	*Phone*	*Fax*
Address		
City	*State/Province*	
Postal Code	*Country*	

5. Reporter ID

Name or ID	*Phone*	*Fax*
Address		
City	*State/Province*	
Postal Code	*Country*	

6. HCP Contact Details (if other than reporter)

Name		
Country		
Address		
City	*State/Province*	*Postal Code*
Phone	*Fax*	

7. Patient

Initials (optional)	*Sex*	*Age (at time of event)*	*Was consent obtained to follow-up with HCP?*
	☐ F ☐ M		☐ Yes ☐ No

Weight	*Height*	*Race*	*Is patient also reporter?*
☐ lbs ☐ kg	☐ in ☐ cm		☐ Yes ☐ No

8. Medical History (include primary diagnosis)

9. Suspect Product Information (include dosing details)

Product/Device: _____

Indication: _____

	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Frequency

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial Size

10. AE, Other Safety Finding, or PC/ADE information — **HCP ONLY**

Finding (List main event first; one event per line)	**Onset Date** (day month year)	**Resolved Date** *(If patient died, list date of death)* ***Cause of Death:*** *(provide autopsy report)* (day month year)	**Hospitalization** Hospitalized? ☐ Yes ☐ No; Prolonged Hospitalization? ☐ Yes ☐ No; Admitting dx _____; **Date Admitted** (day month year)	**Date Discharged** (day month year)	**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 significant medical hazard; 07 Non serious	**Action Taken** 1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=drug rechallenge (state outcome)	**Outcome** 01 Recovered/ Resolved; 02 Recovering/ Resolving; 03 Not recovered/not resolved; 04 Recovered/ resolved with sequelae; 05 Fatal; 06 Unknown	**Severity** 1=mild 2=moderate 3=severe	**Relationship to Product/Device** Is there a reasonable possibility that this event may have been caused by the Product/Device? Product	Device
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N

11. Concomitant Medications (eg, chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	 Yes	Continuing No	 Yes	Dose	Route	Frequency	Treatment Meds

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year	Test										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	Additional Tests	Results	Units

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).

Appendix D. Additional Safety Reporting Information

Adverse Event Severity Scoring System

The latest version of the Common Terminology Criteria for Adverse Events (CTCAE) should be used. The CTCAE is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Appendix E. Pregnancy and Lactation Notification Worksheets

20180062. Pregnancy notification form_2.pd

20180062. Lactation notification form_2.pd

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: 20180062

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:** _____

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: 20180062

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:** _____

Appendix F. Patient Education Materials

Imlygic Information
for patients and clo:

Patient Education
European Union Pat

IMLYGIC®▼: INFORMATION FOR PATIENTS AND CLOSE CONTACTS

This brochure contains important safety information you should know before and during Imlygic® treatment. Please read this information carefully before and after each treatment. Please also read the Imlygic® Package Leaflet that will be handed to you by your healthcare professional. Talk to your doctor or nurse if you have any questions or concerns about your treatment.

What Should I Know About Imlygic®?

- Imlygic® is a weakened form of herpes simplex virus type 1 (HSV-1), which is commonly called the cold sore virus.
- Imlygic® may cause life-threatening herpes infection in persons with weakened immune systems.
- Imlygic® may harm your unborn baby. Tell your doctor if you are pregnant or plan to become pregnant.
- During or after Imlygic® treatment, you could develop cold sores or a more serious herpes infection.
- Imlygic® virus could be spread to your close contacts (household members, caregivers, sex partners, or someone you share a bed with) if they have direct contact with your body fluids or injection sites.
- You should share this information with your close contacts, particularly if they are pregnant or have a weakened immune system.
- Injected sites should be covered with airtight and watertight dressings at all times. Apply the dressing as instructed by your healthcare professional. If the dressing comes loose or falls off, replace it right away with a clean dressing.

This sheet does not include all the important safety information you need to know about Imlygic®. Please refer to the Imlygic® Package Leaflet that will be handed to you by your healthcare professional for more information.
You should read this at the time of each injection because the information may change over time.

What Are Signs and Symptoms of Herpes Infection?

- Pain, burning or tingling in a blister around the mouth or genitals (eg, cold sore), or on the finger or ears with or without a scab
- Eye pain, light sensitivity, discharge from the eyes, redness of eye, tearing, or blurry vision
- Weakness in arms or legs
- Extreme drowsiness (feeling sleepy)
- Fever associated with headache
- Vomiting
- Mental confusion
- Memory loss
- Seizures

If you have any of these symptoms during or after treatment with Imlygic®, tell your doctor right away.

What should I do to avoid spreading Imlygic®?

- Avoid direct contact between injection sites or body fluids of patients and close contacts:
    - The treated patient should minimize the risk of exposure of blood and body fluids to close contacts for the duration of Imlygic® treatment through 30 days after the last administration of Imlygic®. The following activities should be avoided:
        - Sexual intercourse without a latex condom
        - Kissing if either of you has an open mouth sore
        - Common usage of cutlery, crockery, and drinking vessels
        - Common usage of injection needles, razorblades, and toothbrushes

- Avoid touching or scratching the injection sites.
- Keep injection sites covered with airtight and watertight dressings at all times. If the injection site is weeping or oozing, keep the dressing on until the weeping or oozing stops. Apply dressing as instructed by your healthcare professional. If the dressing comes loose or falls off, replace it right away with a clean dressing.
- Place all used dressings and cleaning materials in a sealed plastic bag, and throw them away in household waste, to keep household contacts from directly touching them.

This sheet does not include all the important safety information you need to know about Imlygic®. Please refer to the Imlygic® Package Leaflet that will be handed to you by your healthcare professional for more information.
You should read this at the time of each injection because the information may change over time.

What should I tell my close contacts while I am being treated with Imlygic®?

- Avoid direct contact with your body fluids or injection sites.
- Wear gloves while changing your dressing.
- Clean the affected area with soap and water and/or a disinfectant in case of accidental exposure to Imlygic®. If they develop signs or symptoms of herpes infection, you should ask them to call their doctor.

If your close contact is pregnant or has a weakened immune system, they should not change your dressings or clean your injection sites.

Talk with your doctor or nurse if you have any questions about treatment with Imlygic®.

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get {insert local safety contact phone number}.

Always provide the batch number from your Patient Alert Card when reporting side effects.

This sheet does not include all the important safety information you need to know about Imlygic®. Please refer to the Imlygic® Package Leaflet that will be handed to you by your healthcare professional for more information.
You should read this at the time of each injection because the information may change over time.

Imlygic® ▼ Patient Alert Card

Information on the front:

Instructions to provider: A new card is to be completed with the first administration of Imlygic®. Record the batch number for every administration of Imlygic® on this card. Please supply a new card to the patient if needed during treatment.

Patient's Name:

Imlygic® Prescriber's (Doctor's) Name:

Doctor's Phone Number:

Name of Centre/Institution (if applicable):

Start Date of Imlygic® Treatment:

Imlygic® Batch Numbers (Dates Administered):

Product manufacturer and license holder: {insert here}

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get.

You can get more information from:

- Imlygic® Package Leaflet and Patient Safety Brochure
- {insert local medical information number}

Information on the back:

Information for patients: **Please carry this card with you at all times**. Present this card to healthcare professionals (doctor, nurse) upon consultation or hospitalization.

If you or one of your close contacts develops a herpetic lesion (for example cold sore), please call the doctor (name and phone number provided on front). The lesion can be tested to determine if it is caused by Imlygic®. Imlygic® is sensitive to the antiviral drug acyclovir and a possible infection can be treated with this drug as determined by your doctor.

Information for healthcare professionals:

- Imlygic® Summary of Product Characteristics {insert local CA repository or EMA website}
- {insert local medical information number}

IMLYGIC®▼
(talimogene laherparepvec)

PATIENT ALERT CARD

Please carry this card with you at all times.

Present this card to healthcare professionals (doctor, nurse) upon consultation or hospitalisation.

This card should be folded along the dotted lines

Patient's Name: _____

IMLYGIC® Prescriber's (Doctor's) Name: _____

_____

Doctor's Phone Number: _____

Name of Centre/Institution (if applicable): _____

_____

Start Date of IMLYGIC® Treatment: _____

IMLYGIC® Batch Numbers	Dates Administered

Product Manufacturer and License Holder: _____

Version 1.0

Approved: Month-Year

IMLYGIC®▼

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get {insert contact details/phone number for NCA and local Safety}

You can get more information from:
IMLYGIC® Package Leaflet
and Patient Safety Brochure
{insert local medical information number}

If you or one of your close contacts develops a herpetic lesion (for example cold sore), please call the doctor (name and phone number provided on front).

The lesion can be tested to determine if it is caused by IMLYGIC®. IMLYGIC® is sensitive to the antiviral drug acyclovir and a possible infection can be treated with this drug as determined by your doctor.

INSTRUCTIONS TO PROVIDER:

A new card is to be completed with the first administration of IMLYGIC®. Record the batch number for every administration of IMLYGIC® on this card. Please supply a new card to the patient if needed during treatment.

INFORMATION FOR HEALTHCARE PROFESSIONALS:

IMLYGIC® Summary of Product Characteristics
{insert local CA repository or EMA website}

{insert local medical information number}

Superseding Amendment 3, version 1.0

Protocol Title: A Cross-sectional Survey to Evaluate Patient Knowledge of Safety Messages Included in the Patient Safety Brochure and Patient Alert Card for IMLYGIC®

Amgen Protocol Number 20180062

Amendment Date: 14 October 2019

Rationale:

The final CHMP assessment for Procedure No. EMEA/H/C/002771OO/0034 was received on 19 September 2019 and concludes that the 20180062 Protocol has sufficiently described the rationale for performing the study to evaluate the effectiveness of the patient-directed aRMMs. No further action is required. This Superseding Amendment 3, version 1.0 is being submitted to seek full approval from ORRG.

In addition, this Superseding Amendment 3, version 1.0 is being submitted to correct for minor administrative changes.

- Inclusion of EU PAS Registry Number: EUPAS31213
- Appendix A: Imlgyic Patient Survey Questionnaire is deleted from the protocol but will be held separately as a standalone document.

Description of Changes:

Global:

Change: Editorial changes (including typographical, grammatical and formatting) have been made throughout the document

Section: Summary Table of Study Protocol

Replace:

EU Post Authorization Study (PAS) Register No	<<Insert Number>>

With:

EU Post Authorization Study (PAS) Register No	**EUPAS31213**

Section 5: Amendments and Updates

Replace:

Amendment or Update No.	**Date**	**Section of Study Protocol**	**Amendment or Update**	**Reason**
1	**11 April 2019**	**See summary of changes**		
2	**17 July 2019**	**See summary of changes**		

With:

Amendment or Update No.	**Date**	**Section of Study Protocol**	**Amendment or Update**	**Reason**
1	11 April 2019	See summary of changes		
2	17 July 2019	See summary of changes		
3	**14 October 2019**	**See summary of changes**		

Section 9.3: Variables

Replace:

The survey questionnaire (Appendix A) includes the following:

With:

The survey questionnaire includes the following:

Section: Appendix A. List of Standalone Documents

Delete: