Summary Table of Study Protocol

Title	Clinical Characteristics of The First IMLYGIC™ Patients With Advanced Melanoma Treated in Routine Clinical Practice, in Selected European Countries
Protocol version identifier	20140413
Date of last version of the protocol	28 October 2016
EU Post Authorisation Study (PAS) Register No	NA
Active Substance	Talimogene laherparepvec (T-VEC)
Medicinal Product	IMLYGIC™
Product Reference	EMEA/H/C/002771
Procedure Number	NA
Marketing Authorisation Holder	Amgen Europe B.V. Minervum 7061 NL-4817 ZK Breda The Netherlands
Joint PASS	No
Research Question and Objectives	Primary Objective: • Characterise patients with melanoma at time of first IMLYGIC™ administration in terms of demographics, melanoma disease history, and clinical characteristics Secondary Objectives: • Describe use of IMLYGIC™ • Describe use of other melanoma treatments prior to and after IMLYGIC™ treatment • Describe clinical outcomes after IMLYGIC™ treatment • Describe physician's decision making process and rationale for prescribing IMLYGIC™
Countries of Study	Target countries may include Austria, Finland, Germany, Sweden, the United Kingdom (UK), and potentially other European countries, as per IMLYGIC™ uptake.
Authors	Amgen: Karly Louie, Pari Parkar, Gerald Downey. UBC: Stella Mokiou, Erwin De Cock.

Marketing Authorisation Holder

Marketing authorisation holder(s)	Amgen Europe B.V. Minervum 7061 NL-4817 ZK Breda The Netherlands
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Investigator's Agreement

I have read the attached protocol entitled "Clinical Characteristics of The First IMLYGIC™ Patients with Advanced Melanoma Treated in Routine Clinical Practice, in Selected European Countries", dated 28 October 2016, 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.

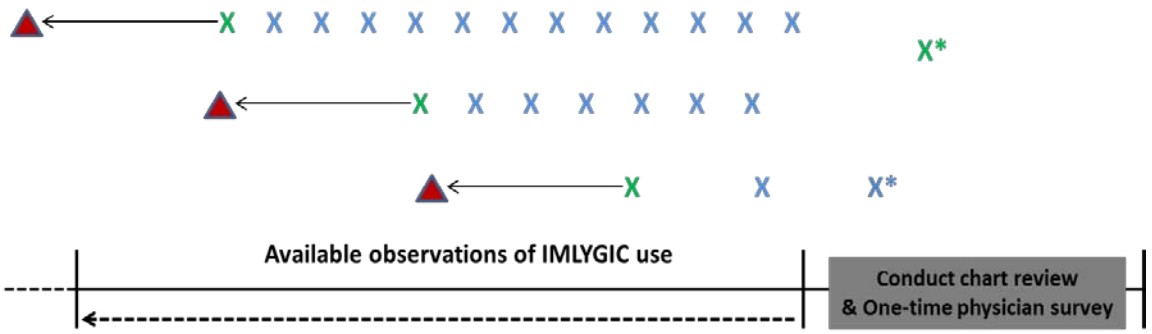
Signature

Name of Investigator

Date (DD Month YYYY)

Study Design Schema

Figure 1. Eligibility and Study Period for Subjects



DATA COLLECTION*

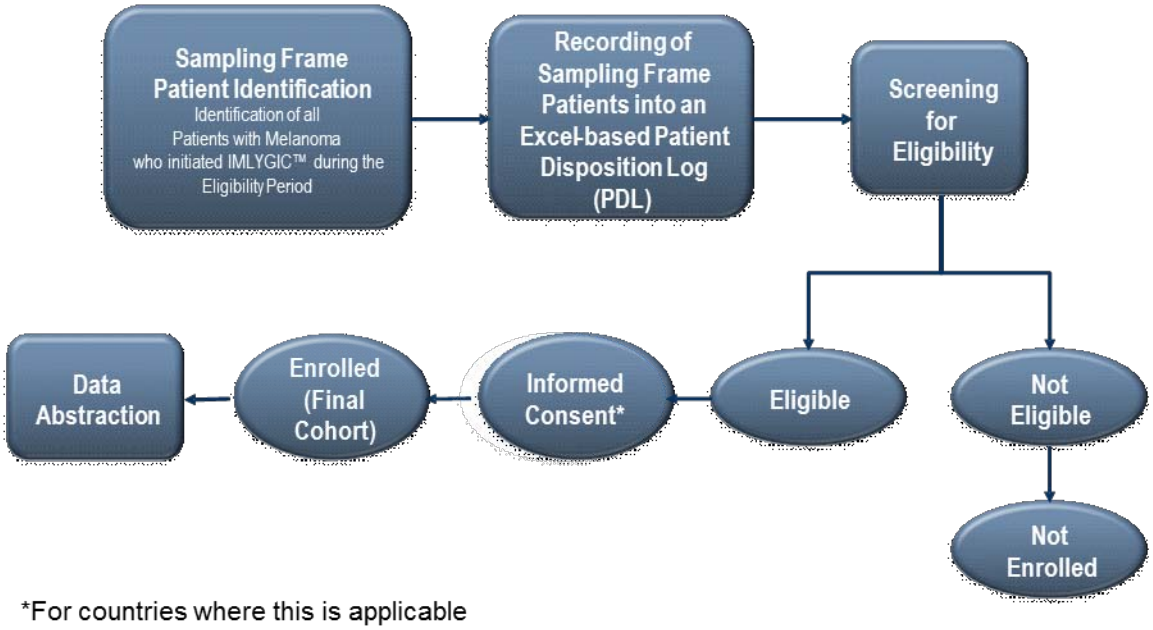
- **First IMLYGIC™ dose**
  - Demographics
  - Melanoma disease history
  - Clinical characteristics
  - Use of IMLYGIC™
  - Use of other melanoma treatment prior to first dose
- **Use of IMLYGIC (up to week 24 following 1st IMLYIGIC™ dose)**
  - Use of IMLYGIC™
  - Use of other melanoma treatment after IMLYGIC™ treatment
  - Concomitant medications
  - Clinical outcomes after IMLYGIC™ treatment

X first dose of IMLYGIC™
melanoma diagnosis
X use of IMLYGIC™ following first dose
X* first dose of IMLYGIC™ after site Initiation - data excluded
X* use of IMLYGIC after site initiation - data excluded

*All events recorded from time melanoma diagnosis to date of site initiation (i.e. start date of data collection)
** Dates are estimated and are subject to change pending IMLYGIC™ uptake and duration of study conduct.

Figure 2. Patient Identification and Enrolment

*For countries where this is applicable.



*For countries where this is applicable

1. Table of Contents

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2. List of Abbreviations

AJCC	American Joint Committee on Cancer
DCF	Data Clarification Form
DRG	Data Review Guidelines
DMP	Data Management Plan
eCRF	electronic Care Report Form
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FDA	Food and Drug Administration
GM-CSF	granulocyte macrophage colony-stimulating factor
HCP	Health Care Provider
HSV	Herpes Simplex Virus
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
ICF	Informed Consent Form
mL	Millilitre
PDL	Patient Disposition Log
PFU	plaque-forming units
SCC	Study Coordinating Centre
SDV	Source Data Verification
T-VEC	Talimogene laherparepvec
UBC	United BioSource Corporation
UK	United Kingdom
US	United States
WHO	World Health Organization

3. Responsible Parties

Role	Contact Details
Sponsor	Amgen Limited 1 Uxbridge Business Park Sanderson Rd Uxbridge UB8 1DH
SCC	United BioSource LLC 920 Harvest Drive, Suite 200 Blue Bell, Pennsylvania 19422 United States of America
Principal Investigator	Dr Mark Harries Guys and St Thomas's Hospital Medical Oncology Management Office 4th Wing Guy's Hospital Great Maze Pond London SE1 9 RT

4. Abstract

- Study Title: Clinical Characteristics of The First IMLYGIC™ Patients with Advanced Melanoma Treated in Routine Clinical Practice, in Selected European Countries
- Study Background and Rationale: Malignant melanoma has the fastest growing incidence of any cancer among men, and the second fastest growing incidence among women in Europe and the United States (US) (IARC, 2012; Howlader, 2016). Talimogene laherparepvec or T-VEC (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 antitumor immune responses. IMLYGIC™ is injected directly into melanoma lesions. Based on positive results from a randomized open-label phase III trial (OPTiM) in patients with unresectable stage IIIB/C and IV melanoma (Andtbacka et al, 2015), Amgen Received European Medicines Agency (EMA) approval for IMLYGIC™ on 17 December 2015 for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a). However, the treatment landscape for melanoma (including targeted and immunotherapies) continues to evolve rapidly. There is a lack of real world data outside clinical trials describing patient characteristics, disease stage and previous melanoma treatments in patients who are prescribed IMLYGIC™. Furthermore, there is also a need to understand physician's prescribing behaviour and rationale for choosing IMLYGIC™. Real-world data are thus warranted to inform on the use of IMLYGIC™ in clinical practice, per the EU marketing authorisation.
- Research Question and Objectives:
  - Primary Objective
    - Characterise patients with melanoma at time of first IMLYGIC™ administration in terms of demographics, melanoma disease history, and clinical characteristics

- Secondary Objectives
  - Describe use of IMLYGIC™
  - Describe use of other melanoma treatments prior to and after IMLYGIC™ treatment
  - Describe clinical outcomes after treatment with IMLYGIC™
  - Describe physician's decision making process and rationale for prescribing IMLYGIC™
- Hypothesis/Estimation
  - A formal hypothesis is not applicable to this study design which is descriptive in nature.

- Study Design/Type: This is a multi-national, multi-centre observational retrospective chart review study with one-time physician survey.
- Study Population or Data Resource: This study will be conducted in up to 10 sites[a] in selected European countries. Target countries may include Austria, Finland, Germany, Sweden, the United Kingdom (UK), and potentially other European countries.[b] A site will be considered a candidate for participation when they have at least one IMLYGIC™ treated patient. The eligibility period for identifying suitable patients is from the date of IMLYGIC™ EMA approval (17 December 2015) to the date of site initiation to allow for the accrual of up to 30 subjects across all sites (target sample size of approximately 2 to 5 subjects per site). The study population will consist of melanoma patients who received at least one IMLYGIC™ injection. Data will be collected retrospectively from patient medical charts spanning the date of melanoma diagnosis to the date of site initiation (ie, start date of data collection). Physician's IMLYGIC™ decision making process and rationale for prescribing will be captured in a one-time survey.
- Summary of Subject Eligibility Criteria:
  - Inclusion Criteria
    - Patient has a diagnosis of unresectable melanoma stage IIIB, IIIC, or IVM1a, received at least one IMLYGIC™ dose as per the EU marketing authorisation during the study eligibility period, was 18 years of age or older at the time of first IMLYGIC™ administration, and patient/legal representative provided written informed consent, where required.
  - Exclusion Criteria
    - Patient has ever received IMLYGIC™ as part of a clinical trial or expanded access program; presence of bone, brain, lung, or other visceral disease at time of first IMLYGIC™ administration; or patient's medical chart is not available for data abstraction.

[a] More than 10 sites may be considered if and only if 10 sites cannot contribute up to 30 subjects to this study.
[b] The aim is to include at least 3 countries; the final number of selected countries and the total number of sites enrolled into the study will depend on IMLYGIC™ uptake in the selected countries and the volume of potentially eligible patients that each site can contribute to this study.

- Variables:
  - Patient demographics
  - Melanoma disease history
  - Clinical characteristics at first IMLYGIC™ administration
  - Use of IMLYGIC™
  - Use of other melanoma treatment(s) prior to and after IMLYGIC™ treatment
  - Clinical outcomes after treatment with IMLYGIC™
  - Physician's decision making process and rationale for prescribing IMLYGIC™
- Study Sample Size: Convenience sampling will be employed for a total target sample of up to 30 medical chart reviews (target of 2 to 5 charts per site)[c]. Precision per study sample size has been provided in Section 9.5.
- Data Analysis: Analysis will be descriptive with appropriate statistical methods (ie, mean, standard deviation, median, quartiles, minimum and maximum for continuous variables; numbers and percentages for categorical variables).

5. Amendments and Updates

None

6. Milestones

Milestone	Planned date*
Start of data collection	February 2017
End of data collection	April 2017
Final report of study results	June/July 2017

*These are planned timelines that may be subject to change based on the rate of IMLYGIC™ uptake in target EU countries.

7. Background and Rationale

7.1 Diseases and Therapeutic Area

The World Health Organisation (WHO) reported that every year, more than 100,000 new cases of melanoma are diagnosed and there are more than 23,000 deaths in Europe (IARC, 2012). At a time when the incidence of most cancers are falling, the incidence of melanoma is increasing at an annual rate of 3-7% in many European countries (IARC, 2012). Incidence rates of melanoma vary greatly across Europe, ranging between 1.3 in Albania to 25.8 per 100,000 people in Switzerland (IARC, 2012).

Surgery is an effective treatment for controlling local disease (stage I and II), and is also the standard of care for regional disease (stage III). Furthermore, it is an option for some melanoma patients with distant (stage IV) disease (NCCN, 2016). Stage of disease at

[c] Site sample size is variable and dependent on the availability of eligible patients.

diagnosis is the strongest predictive factor for survival in melanoma. The American Joint Committee on Cancer (AJCC) Melanoma Staging system is widely accepted as a useful prognostic indicator (Balch et al, 2009), 5-year survival for stage IIIA melanoma patients is 65-70%, 40-60% for stage IIIB, 20-35% for stage IIIC, 30% for stage IVM1a, 20% for stage IVM1b and finally 10% for stage IVM1c patients (FDA, 2015).

During the last five years the therapeutic landscape for patients with advanced (unresectable or metastatic) melanoma has changed rapidly to currently include different systemic therapies such as chemotherapy, targeted agents and immunotherapy. Approved therapies for advanced melanoma are: ipilimumab (Yervoy), nivolumab (Opdivo), and pembrolizumab (Keytruda). For patients with unresectable or metastatic melanoma and BRAF V600E mutations targeted agents vemurafenib (Zelboraf), dabrafenib (Tafinlar), trametinib (Mekinist) are available. Patients with unresectable or metastatic melanoma with disease progression following ipilimumab and/or BRAF/MEK inhibitors are treated with pembrolizumab (Keytruda) and nivolumab (Opdivo) (NCCN, 2016).

Talimogene laherparepvec or T-VEC (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 antitumor immune responses. IMLYGIC™ is injected directly into melanoma lesions (Harrington et al, 2015). IMLYGIC™ was compared with subcutaneously administered GM-CSF in patients with unresectable stage IIIB/C and IV melanoma in a randomized open-label phase III trial (OPTiM), that included sites in Canada, South Africa, US and the UK (Andtbacka et al, 2015). Based on positive results from this phase III trial, Amgen received FDA approval for IMLYGIC™ indicated for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial therapy on 27 October 2015. On 17 December 2015, the EMA also approved IMLYGIC™ 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 administered by injection into injectable cutaneous, subcutaneous, and nodal lesions that are visible, palpable, or detectable by ultrasound guidance. IMLYGIC™ is provided in single-use vials of 1 mL each in two different dose strengths: 10^6 (1 million) plaque-forming units (PFU) per mL for the initial treatment visit only and

10^8 (100 million) PFU per mL for all subsequent treatment visits. The volume of IMLYGLIC™ to be injected into each lesion is dependent on the size of the lesion. The total injection volume for each treatment session should be up to a maximum of 4 mL. It may not be possible to inject all lesions at each treatment visit or over the full course of the treatment. Previously injected and uninjected lesions may be injected at subsequent treatment visits. The recommended dosing schedule is the initial treatment visit, a second treatment visit at three weeks after initial treatment, and all subsequent treatment visits at two-week intervals.

7.2 Rationale

The OPTiM trial enrolled patients between May 2009 and July 2011 and since then new regimens have been approved for unresectable and metastatic melanoma including immunotherapies and targeted therapies. GM-CSF was selected as a comparator to IMLYGIC™ in the OPTiM trial based on its immune-mediated mechanism of action, established safety profile and preliminary evidence of clinical benefit as adjuvant therapy in resectable stage III to IV melanoma. The new therapies have changed the standard of care for unresectable and metastatic melanoma and improved overall survival. There is a lack of real-world data outside clinical trials describing patient characteristics, disease stage and previous melanoma treatments in patients who are prescribed IMLYGIC™. Real-world data are thus warranted to inform on clinical practice with regards to initial IMLYGIC™ use in the current therapeutic landscape of unresectable and metastatic melanoma.

7.3 Statistical Inference (Estimation or Hypothesis)

A formal hypothesis does not apply to this study.

The study will collect and descriptively report information on demographics, melanoma disease history, clinical characteristics, use of IMLYGIC™, use of other melanoma treatments prior to and after IMLYGIC™ treatment, and clinical outcomes following IMLYGIC™ treatment. Additionally, it will describe the physician's decision making process and rationale for prescribing IMLYGIC™.

8. Research Question and Objectives

8.1 Primary

- Characterise patients with melanoma at time of first IMLYGIC™ dose in terms of demographics, melanoma disease history, and clinical characteristics.

8.2 Secondary

- Describe use of IMLYGIC™
- Describe use of other melanoma treatments prior to and after IMLYGIC™ treatment
- Describe clinical outcomes after treatment with IMLYGIC™
- Describe physician's decision making process and rationale for prescribing IMLYGIC™

9. Research Methods

9.1 Study Design

This is a multi-national, multi-centre observational retrospective chart review complemented by a one-time physician survey. This study will be conducted in up to 10 sites[d] in selected European countries. Target countries may include Austria, Finland, Germany, Sweden, the United Kingdom (UK), and potentially other European countries.[e] Medical charts from up to 30 eligible patients across all sites will be abstracted. A chart review study design was chosen in order to collect real-world data to characterise the first patients receiving IMLYGIC™ following EU market authorization. Data will be collected retrospectively from patient medical charts spanning the date of melanoma diagnosis to the date of site initiation (ie, start date of data collection). There will be no prospective data collection from the date of site initiation onwards. Physician's IMLYGIC™ prescribing behaviour and rationale will be captured in a one-time survey.

This study involves no intervention and does not interfere with usual medical care, and thus it will not affect patient treatment. There will be no direct patient contact for this study. The study is sponsored by Amgen, hereinafter referred to as the Sponsor. The study will be managed by United BioSource Corporation (UBC), hereinafter referred to as the Study Coordinating Centre (SCC). No patient-identifying information will be transferred to the Sponsor or the SCC.

Local site study staff will identify a sampling frame of potentially eligible patients with melanoma who received at least one IMLYGIC™ injection during the eligibility period (from date of EMA IMLYGIC™ approval, 17 December 2015, to date of site initiation). Each of these identified patients will be entered into a spreadsheet-based patient disposition log (PDL) and will be assigned a pre-formatted unique study identification

[d] More than 10 sites may be considered if and only if 10 sites cannot contribute up to 30 subjects to this study.

[e] The aim is to include at least 3 countries; the final number of selected countries and the total number of sites enrolled into the study will depend on IMLYGIC™ uptake in the selected countries and the volume of potentially eligible patients that each site can contribute to this study.

number. Once all patients who comprise the sampling frame have been identified and recorded in the PDL, trained site staff will access the medical charts for each of them in order to confirm study eligibility criteria. If all eligibility criteria are met, the patients selected will comprise the final study cohort and will be enrolled into the study as subjects and have their medical charts reviewed, provided informed consent has been obtained. The target sample size is approximately 2 to 5 subjects per site, but the final sample size per site will depend on the availability of eligible melanoma patients receiving IMLYGIC™ therapy during the eligibility period.

9.2 Setting and Study Population

9.2.1 Study Period

Eligibility period

The eligibility period duration starts from the date of IMLYGIC™ EMA approval on 17 December 2015 to date of site initiation (ie, start date of data collection) to allow for the accrual of up to 30 subjects.

Study period

The study period for retrospective data abstraction is the period of time within which study data will be collected for each subject. The study period spans from the date of melanoma diagnosis to date of site initiation. The date of melanoma diagnosis could be prior to the date of EMA approval on 17 December 2015.

9.2.2 Selection and Number of Sites

This study will be conducted in up to 10 sites[f] in selected European countries. Target countries may include Austria, Finland, Germany, Sweden, the United Kingdom (UK), and potentially other European countries.[g] SCC will closely monitor the country-specific IMLYGIC™ uptake and will employ continuous feasibility performance to assess country and site suitability. A structured assessment questionnaire will be administered to each potential site as part of the formal site qualification process. A site needs to have at least one IMLYGIC™ treated patient prior to study initiation in order to participate. Prior to chart abstraction initiation, following ethics approval and site contract execution,

[f] More than 10 sites may be considered if 10 sites alone cannot contribute up to 30 subjects to this study.

[g] The aim is to include at least 3 countries; the final number of selected countries and the total number of sites enrolled into the study will depend on IMLYGIC™ uptake in the selected countries and the volume of potentially eligible patients that each site can contribute to this study.

participating sites will be trained on the study protocol, electronic case report form (eCRF) completion, and data management procedures.

9.2.3 Subject Eligibility

9.2.3.1 Inclusion Criteria

- Patient has a diagnosis of unresectable melanoma stage IIIB, IIIC, or IVM1a prior to receiving the first IMLYGIC™ dose documented in the medical chart
- Patient received at least one IMLYGIC™ dose as per the EU marketing authorisation at one of the participating study sites during the study eligibility period (period spanning 17 December 2015 to site initiation).
- Patient was 18 years of age or older at the time of first IMLYGIC™ administration, per the EU marketing authorisation.
- Patient or a legal representative written consent for access to medical chart is obtained, where required.

9.2.3.2 Exclusion Criteria

- Patient has ever received IMLYGIC™ as part of a clinical trial or expanded access program.
- Patients with bone, brain, lung or other visceral disease at time of first IMLYGIC™ administration will be excluded
- Patient's medical chart is not available for data abstraction.

9.2.4 One-time Physician Survey

- At each site, eligible health care providers (HCPs) are those physicians who have experience in administering and/or prescribing IMLYGIC™. There could be more than one eligible HCP per site. Approximately 10 HCPs will participate in the one-time survey.

9.2.5 Matching

Not applicable for this study.

9.2.6 Baseline Period

Not applicable for this study. Data will be collected retrospectively from patient medical charts spanning the date of melanoma diagnosis to the date of site initiation (ie, start date of data collection).

9.2.7 Study Follow-up

Not applicable for this study (retrospective data collection only).

9.3 Variables

Data will be abstracts from medical charts and will also come from a one-time physician survey.

At time of first IMLYGIC™ dose, variables in the following categories will be collected:

- Patient demographics
- Melanoma disease history
- Clinical characteristics at first IMLYGIC™ administration
- Use of IMLYGIC™
- Use of other melanoma treatment(s) prior to IMLYGIC™ treatment

Variables in the following categories will be collected on use of IMLYGIC™ up to 24 weeks following the first dose if data are available within the study period:

- Use of IMLYGIC™
- Use of other melanoma(s) treatment after IMLYGIC™ treatment
- Concomitant medication(s)
- Clinical outcomes after IMLYGIC™ treatment

Variables in the following categories will be collected to understand the physician's decision making process and rationale for prescribing IMLYGIC™ from the one-time physician survey:

- Physician characteristics
- Treatment practices of patients with unresectable melanoma stage IIIB, IIIC and IVM1a
- Treatment practices with IMLYGIC™

9.3.1 Exposure Assessment

Not applicable for this study.

9.3.2 Outcome Assessment

All the variables that constitute the outcomes for the IMLYGIC™ patient for this study are detailed below in Table 1.

Table 1. Outcome Variables Collected From Patient Chart Review

Parameter type	Variable
Demographics	
	sex
	age at first IMLYGIC™ administration
Melanoma disease history	
Primary melanoma diagnosis (initial diagnosis) and diagnosis prior to first IMLYGIC™ dose	
	date of biopsy
	disease stage (TNM Classification of Malignant Tumours)
	body site of lesion(s)
	number of lesions
	size of lesion(s)
Clinical characteristics at time of first IMLYGIC™ dose[a]	
	ECOG performance status
	ECOG date reported
	BRAF status
	serum lactate dehydrogenase status
	HSV serostatus
Tumour characteristics at first IMLYGIC™ dose[a]	
	Cutaneous lesions (yes, no unknown)
	If YES, for each cutaneous lesion,
	*anatomical region (head/neck, trunk, upper extremity, lower extremity)
	*diameter of lesion (cm)
	*lesion injected (yes, no, unknown)
	Subcutaneous lesions (yes, no, unknown)
	If YES, for each subcutaneous lesion,
	*anatomical region (head/neck, trunk, upper extremity, lower extremity)
	*diameter of lesion (cm)
	*lesion injected (yes, no, unknown)
	Nodal lesions (yes, no, unknown)
	If YES, for each nodal lesion,
	*anatomical region (axillary, cervical, inguinal, other)
	*diameter of lesion (cm)
	*lesion injected (yes, no, unknown)

[a] last reported prior to dose of IMLYGIC™ and date reported
[b] Include all records recorded within the study period

Table 1. Outcome Variables Collected From Patient Chart Review

Parameter type	Variable
Use of IMLYGIC™ (up to 24 weeks, equivalent to 13 doses)	
	date(s) of injection
	concentration of preparation (10^6 or 10^8 PFU)
	injected volume
	reason for discontinuation of IMLYGIC™
	date of recorded reason for discontinuation
	date of planned IMLYGIC™ treatment (if outside study period)
Other melanoma treatment[‡] prior to and after IMLYGIC™ treatment	
	Use of melanoma lesion surgery (yes, no, unknown)
	*procedure type and date(s) of surgery
	Use of lymph node surgery (yes, no, unknown)
	*type of lymphadenectomy and date(s) of lymph node surgery
	Local therapy
	*type of local therapy and date(s) of local therapy
	*type of planned local therapy and date(s) of planned local therapy
	*reason for discontinuation of local therapy
	Regional therapy (yes, no, unknown)
	*type of regional therapy and date(s) of regional therapy
	*type of planned regional therapy and date(s) of planned regional therapy
	*reason for discontinuation of regional therapy
	Systemic therapy (yes, no, unknown)
	*type of systemic therapy and start and end date(s) of systemic therapy
	*planned systemic therapy and date(s) of planned systemic therapy
	*Reason for discontinuation of systemic therapy
	Adjuvant therapy (yes, no, unknown)
	*type of adjuvant therapy and date(s) of adjuvant therapy
	*planned type of adjuvant therapy and date(s) of planned adjuvant therapy
Concomitant Medications	
	use of anti-herpetic viral agent and start and end date(s) of anti-herpetic viral agent

[a] last reported prior to dose of IMLYGIC™ and date reported
[b] Include all records recorded within the study period

Table 1. Outcome Variables Collected From Patient Chart Review

Parameter type	Variable
Clinical outcomes[b]	
	events of interest (distant metastasis, herpetic events, immune-mediate events, injection site complications) and date(s) of events of interest
	Date of death (if applicable) or date of last known clinic visit
	*If death occurred, primary cause of death
	survival status at end of study period (alive or dead)

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[a] last reported prior to dose of IMLYGIC™ and date reported
[b] Include all records recorded within the study period

All the variables that constitute the outcomes from the Physician Survey are detailed below in Table 2:

Table 2. Outcome Variables Collected From the Physician Survey

Parameter type	Variable
Physician characteristics	
	sex
	type of hospital/clinic
	primary and secondary medical specialty
	Years of experience working with melanoma patients
Treatment practices of patients with unresectable melanoma stage IIIB, IIIC and IVM1a	
	distribution of melanoma patients treated by stage
	factors that make patients ineligible for resection
	BRAF status of patients
	types of melanoma treatments used to treat patients according to stage of disease
	reasons for not using systemic drug treatment
	prescribing practices of immunotherapy, targeted therapy, oncolytic viral therapy, combination therapy or other (ever or currently use)
	Treatment pathways used
Treatment practices with IMLYGIC™	
	use of IMLYGIC™ as prescriber, administrator or both
	IMLYGIC™ treatment duration
	setting used for treatment (clinical trial, expanded access programme, routine clinical practice)
	no. of patients treated with IMLYGIC™
	average duration of IMLYGIC™ treatment
	factors that determine how many melanoma lesions are injected
	factors that determine use of ultrasound guidance to inject IMLYGIC™
	factors that influence (treatment attributes, safety, access considerations, patient characteristics and personal experience) choice of IMLYGIC™
	factors that make patients with unresectable stage IIIB, IIIC and IVM1a ineligible for IMLYGIC™
	challenges in treating patients with IMLYGIC™

9.3.3 Covariate Assessment

Not applicable for this study.

9.3.4 Validity and Reliability

Internal validity of study design

Study data, generated from patient medical charts, are subject to missing data and errors from missing charts, unrecorded information, variance in recorded information by practice and medical staff, difficulty in interpreting information (eg, jargon, acronyms), and no outside verification of information. An additional limitation is that information about a subjects' treatment outside of the specific cancer care site may not be captured in the available medical chart.

External validity of study design

Generalizability of study results may be limited by use of a convenience (ie, not random) sample of subjects, hence the subjects and treatment patterns observed in this study may not completely reflect the real-world population of patients receiving IMLYGIC™. In addition, at sites where patient informed consent is required to access medical charts, a patient consenting may be different than a patient not consenting, resulting in potential selection bias. An additional risk for external validity is that the utility of results may be limited given the rapidly evolving therapeutic landscape in melanoma.

9.4 Data Sources

The data sources for this study are:

- Hospital medical charts. These charts can include a combination of paper and electronic charts that are kept at the participating study sites. The type of medical charts kept at study sites is site-specific. Prior to the study start sites will determine which charts they need to access in order to provide the required data. Most sites may have one comprehensive clinical chart that contains all the information on patient care within the site but some sites may have charts dispersed within different departments. Prior to site initiation, the chart(s) required will be identified and made available for abstraction.
- One-time physician survey. One or more eligible HCPs at each site will complete a one-time survey during study conduct to assess their decision making process and rationale for prescribing IMLYGIC™.

9.5 Study Size

Overall, the total target sample size is approximately 15 to 30 subjects with melanoma who have received at least one IMLYGIC™ administration outside of clinical trial or expanded access program settings in selected European countries. Approximately 10 HCPs will complete the one-time physician survey. Convenience sampling will be employed. Since this is a small study with descriptive objectives, the precision that this

study will have in estimating a binomial proportion is based on Wilson's score method (no continuity correction) and the maximum half-width of the 95% confidence interval (Brown et al, 2001) will be 25% and 18% for a sample size of 15 or 30 subjects respectively; and 31% for 10 HCPs.

9.6 Data Management

Data will be abstracted from patient medical charts and entered into an Excel-based electronic CRF (eCRF) by site study staff. At study outset, all patients who received at least one IMLYGIC™ administration as melanoma therapy during the eligibility period will be assigned a unique study identification number. There will be no formal source data verification (SDV) as data collected will be pseudonymised (anonymous) to non-site staff. Updates to the Excel eCRFs will be documented through the use of paper-based data clarification forms (DCFs).

It is the responsibility of the site study staff to ensure that the data are as accurate and complete as possible. Once data are deemed clean just prior to database lock, the investigator from each site will sign-off on a pdf version of the Excel-based eCRF to attest that data have been verified and are complete and accurate as per data source (patient medical charts). The SCC will oversee and monitor the entry of de-identified data into Excel-based eCRFs by site staff. The SCC will monitor site performance and intervene to anticipate or manage problems and raise or respond to queries as necessary.

All requested information must be entered on the eCRFs in the spaces provided. If an item is not available or is not applicable, it should be documented as such. Protocol training and procedures for filling out the Excel-based eCRF will be provided through WebEx training sessions. Procedures for patient identification, screening, data entry and query resolution will be documented in a training manual. The SCC will provide support to site study staff experiencing eCRF completion difficulties.

One or more eligible HCPs at each site will complete a one-time physician survey to assess their decision making process and rationale for prescribing IMLYGIC™ in parallel with patient-level data abstraction. The survey can be completed electronically or by hand and each HCP will sign-off on the survey to attest to information accuracy. Survey responses will be entered into an Excel spreadsheet by the SCC prior to database lock.

The study staff will be responsible for uploading the Excel-based eCRF and one-time survey to the secured study portal and the SCC will be responsible for securely transferring the final Excel datasets to the study Sponsor post-database lock. Further details regarding the monitoring, cleaning and locking and archiving of the data, which will include a quality control check-list, will be in a Data Management Plan (DMP).

9.6.1 Review and Verification of Data Quality

Data will be quality controlled by UBC on the basis of pre-specified data review guidelines (DRGs). Basic validation rules will be built into the Excel-based eCRF prior to data abstraction commencement at the sites (eg, drop down lists). All data discrepancies identified during data review will be issued to study sites for resolution using DCFs. All outstanding queries within the data will be reconciled prior to database lock to ensure a complete and quality controlled dataset is ready for analyses. The investigator and study staff agree to cooperate with the SCC to ensure that any discrepancies detected over the course of the eCRF completion are resolved. UBC will monitor site performance remotely and intervene to anticipate or manage problems and raise or respond to queries as necessary.

9.7 Data Analysis

9.7.1 Planned Analyses

Summary statistics for continuous variables (mean, standard deviation, median, quartiles, minimum and maximum) and for categorical variables (numbers and percentages) will be presented based on all participating subjects.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

This is a descriptive study with no pre-specified research hypotheses to be tested.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

All analyses will be based on the abstracted data and one-time physician survey data.

There are no plans for the substitution/imputation of missing values.

Lost to follow-up is not an issue as this is a retrospective data collection study with no prospective data collection following date of site initiation onwards.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrolment

All patients who received at least one IMLYGIC™ administration as melanoma therapy during the eligibility period, from the date of IMLYGIC™ EMA approval (17 December 2015) to the date of site initiation, will be identified by site staff at each of the study sites, to allow for the accrual of up to 30 subjects.

9.7.2.3.2 Description of Subject/Patient Characteristics

Patients with melanoma, aged 18 years of age or older, who received at least one IMLYGIC™ administration as therapy during the eligibility period outside of a clinical trial or expanded access program setting, who do not have bone, brain, lung and other visceral disease at time of first IMLYGIC™ administration, and who provided informed consent for their medical data to be abstracted (where applicable), will be selected for eligibility assessment.

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

The analysis of the data will be descriptive with appropriate statistical methods (ie, mean, standard deviation, median, quartiles, minimum and maximum for continuous variables; numbers and percentages for categorical variables).

9.7.2.5 Sensitivity Analysis

Not applicable for this study.

9.7.2.5.1 Subgroup Analysis

Not applicable for this study.

9.7.2.5.2 Stratified Analysis

Not applicable for this study.

9.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable for this study.

9.7.2.5.4 Other Sensitivity Analysis

Not applicable for this study.

9.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Not applicable for this study.

9.8 Quality Control

Before the first chart abstraction is undertaken, the SCC or delegate will:

- Determine each investigator's capability to appropriately undertake this study.
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regards to protocol compliance, and the responsibilities of the Sponsor or its representatives and the SCC.

During the study, the SCC will keep in regular contact with the sites by:

- Providing information and support to the investigator(s) and other personnel involved with the study.
- Confirming that the research team is complying with the protocol and that data are being accurately recorded in the eCRFs.
- Ensuring that the eCRFs are completed properly and with adequate quality.

Furthermore, the Excel-based eCRF will be built in a way to allow for basic validation methods prior to data abstraction commencement at the sites (eg, drop down lists and value range controls). However, a data cleaning method will furthermore be employed in order to correct inconsistencies or errors that were not captured during data entry (eg, outliers or conflicting data). Data will be clarified with the sites by DCF. All queries and their reconciliations will be documented and an audit trail of any changes will be kept on file. There will be no formal SDV. SCC will monitor site performance remotely and intervene to anticipate or manage problems and raise or respond to queries as necessary.

Investigators shall retain study records for the maximum period required by national regulations or the Institution in which the study is conducted. Study records include the identity of all participating subjects (sufficient information to link records, eg, eCRFs and medical charts), all original signed informed consent forms (ICFs) (if applicable), copies of all eCRFs, and source documents. If the investigator becomes unable for any reason (eg, retirement or relocation) to continue to retain the study records for the required period, the Sponsor should be notified. The study records must be transferred to a designee acceptable to Sponsor, such as another investigator, another institution, or to an independent third party arranged by the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

9.9 Limitations of the Research Methods

Due to the nature of a retrospective study design, the data abstraction can be compromised by the availability, completeness and accuracy of medical charts, as well as the variability in the information collected by different observers. Data availability will be assessed during site qualification for this study via a feasibility survey. Drop down lists programmed into the Excel-based eCRF will demonstrate to sites what information is requested to streamline data collection. Accuracy and consistency of data records will be controlled at data entry point by means of basic validation methods built into the eCRF. It is also noted that due to the initial uptake stage of the drug and the resulting small number of available patients, the resulting profile of patients using IMLYGIC™ as melanoma therapy might not be fully representative of future use. The main limitation of the HCP survey is that it will generate mostly qualitative information from a small number of HCPs across the participating sites.

9.9.1 Information Bias

All site staff that will be abstracting data will be provided systematic training to limit variability in the data abstraction process and, as such, to limit information bias.

9.9.2 Selection Bias

There is a probability of selection bias (ie, the sample obtained not being representative of the population) since the pool of available sites is currently restricted due to the recent introduction of IMLYGIC™ in clinical practice. As commercial introduction of IMLYGIC™ was initially in private clinical practice, it is possible that there will be a larger proportion of IMLYGIC™ patients enrolled from the private sector than the public sector. These first IMLYGIC™ patients may not be representative of the eligible population in the future when availability of the drug becomes more widespread. Similarly, HCPs who decide to prescribe IMLYGIC™ at the time of drug approval may have different treatment and management practices from HCPs who prescribe later. In order to minimize selection bias, a maximum of 5 patients will be recruited per study site.

9.9.3 Confounding

Not applicable for this study.

9.9.4 Analysis Limitations

This is a descriptive (non-hypothesis-testing) study. Only descriptive statistics will be employed due to the limited number of subjects that will be enrolled. Therefore, no inferences can and will be drawn to the overall population. Results will give early

insights into the characteristics of the patients who participated in this study, but cannot be generalized to the population of patients receiving IMLYGIC™.

The same limitation applies to the physician survey, where early insights into the prescribing behaviour of the HCPs who participated in the survey cannot be generalized to a wider population of physicians prescribing IMLYGIC™.

9.9.4.1 Limitations Due to Missing Data and/or Incomplete Data

Patients whose medical charts are completely missing or empty will be excluded from the study. During training, emphasis will be on complete data extraction and avoiding missing data.

No substitution of missing values will take place.

10. Protection of Human Subjects

This study will comply with all applicable laws, regulations, and guidance regarding subject protection including subject privacy. This non-interventional study is a retrospective medical chart review. The Sponsor will not have access to subject's original medical charts and all data provided to the SCC will be de-identified (anonymised). Where applicable, the investigator is obliged to obtain institutional/local or central Independent Ethics Committees (IECs) approval. There will be no contact required with subjects (aside from consent where needed) and no data linkages required. Central/local IECs approval will be obtained and individual sites may vary in the type of institutional review/approval needed in order to gain access to medical charts.

A copy of the protocol will be submitted to the central/local IEC board for written approval. A copy of the written approval of the protocol and waiver of requirement to obtain informed consent (if required) will be received by the Sponsor or its representatives before the recruitment process begins.

The investigator is also responsible for forwarding the following documents to the SCC for review before study initiation occurs:

- Signed and dated protocol signature page (Investigator Agreement)
- Copy of the central/local IEC Board approval of the protocol, waiver for requirement of informed consent (if required)
- Up-to-date curriculum vitae of investigators and all co/sub-physicians
- Signed confidentiality agreement
- Signed study contract

The investigator has to ensure that the subject's confidentiality is maintained:

- On the eCRFs or other documents submitted to Sponsor and the SCC, subjects should be identified by a patient ID number only
- On documents that are not for submission to the Sponsor or the SCC should be kept in strict confidence by the investigator.

The investigator will be charged with maintaining correct and comprehensive documentation, while the Sponsor and SCC are tasked to ensure that the investigator is following the correct study protocol.

10.1 Informed Consent

Informed consent will be sought if it is required by national or local regulations. This requirement will be verified with National Competent Authorities/IECs and/or sites directly. If data is collected from the medical charts of deceased subjects, the country specific data protection laws will also be consulted to account for this. An abbreviated version of an ICF can be used due to the observational and retrospective nature of the study.

10.2 Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and ICFs, and other relevant documents, (eg, recruitment advertisements), if applicable, from the IEC. All correspondence with the IEC should be retained in the Investigator File. Copies of IEC approvals should be forwarded to Sponsor. The SCC will prepare all central and local IEC submissions where applicable. The study sites will prepare all local IEC submissions and will follow local requirements to obtain the study approval.

10.3 Subject Confidentiality

To safeguard subject confidentiality, the eCRFs will record subjects only by means of an anonymous, unique study identification number assigned by the SCC. No information such as initials, date of birth, or local subject study identification number that could subsequently be used to identify subjects will be entered into the eCRFs. Only investigators, or site personnel delegated by them, will have the possibility of associating the de-identified assigned identification number to a specific subject. The de-identified study identification number will be assigned and used by the SCC throughout the study and only site study staff will be involved in the abstraction of the medical chart data. Although a sampling frame list may be generated at the study sites, this list will be

de-identified prior to its use by the SCC. There will be no SDV to safeguard subject confidentiality.

11. Collection of Safety Information and Product Complaints

Active/solicited reporting of adverse events is not applicable for secondary data collection studies (including retrospective chart review studies).

All safety information (AEs) and product complaints should have been reported spontaneously as per standard practice at the time of occurrence.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

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

The Sponsor reserves the right to terminate the study at any time. Both the Sponsor 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 or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to the Sponsor.

13. Plans for Disseminating and Communicating Study Results

The results of this study will be summarised in a Clinical Study Report.

Results of this study are also intended to be published in a peer-reviewed journal and/ or to be presented at a relevant congress. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- 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, 3 and 4.

- When a large, multicentre 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 as 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 the Sponsor for corporate review. The vendor agreement will detail the procedures for, and timing of the Sponsor's review of publications.

14. References

Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. J Clin Oncol 2015;33(25):2780-8.

Balch CM, Gershenwald JE, Soong SJ, et al. (2009). Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27(36):6199-206.

Brown LD, Cai TT, DasGupta A (2001). Interval estimation for a binomial proportion. Statist Sci 16:101-133 (2001)

FDA. FDA Briefing Document Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee Meeting, 29 April 2015. Assessed 14 April 2016. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM444715.pdf

Harrington KJ, Puzanov I, Hecht JR, et al. Clinical development of talimogene laherparepvec (T-VEC): a modified herpes simplex virus type-1–derived oncolytic immunotherapy. Expert Rev Anticancer Ther 2015;15(12):1389-1403.

Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016

International Agency for Research on Cancer, World Health Organization. European Cancer Observatory (EUCAN), 2012. Cancer Factsheets. Assessed 14 April 2016. Available at: http://eco.iarc.fr/eucan/CancerSearch.aspx

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Melanoma, Version 2.2016.

15. Appendices

None