Summary Table of Study Protocol

Title	Clinical Characteristics of The First IMLYGIC™ Patients With **Unresectable Stage IIIB-IVM1a** 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, Germany, **Netherlands,** the United Kingdom (UK), and potentially other European countries, as per IMLYGIC® uptake.
Authors	Amgen: PPD [redacted] UBC: PPD [redacted]

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 **Unresectable Stage IIIB-IVM1a** Melanoma Treated in Routine Clinical Practice, in Selected European Countries", dated **30 October 2017**, 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.

_____

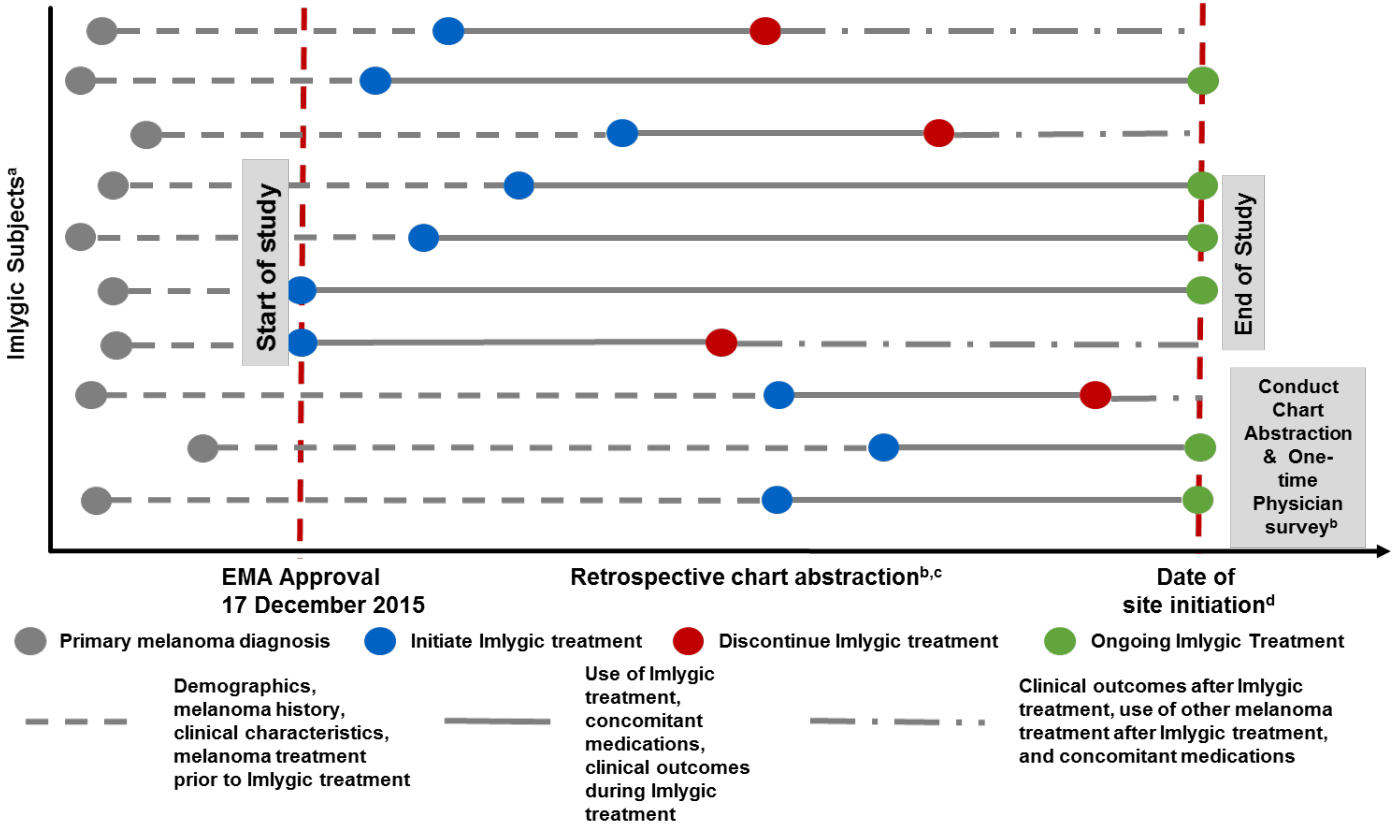
Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

Study Design Schema

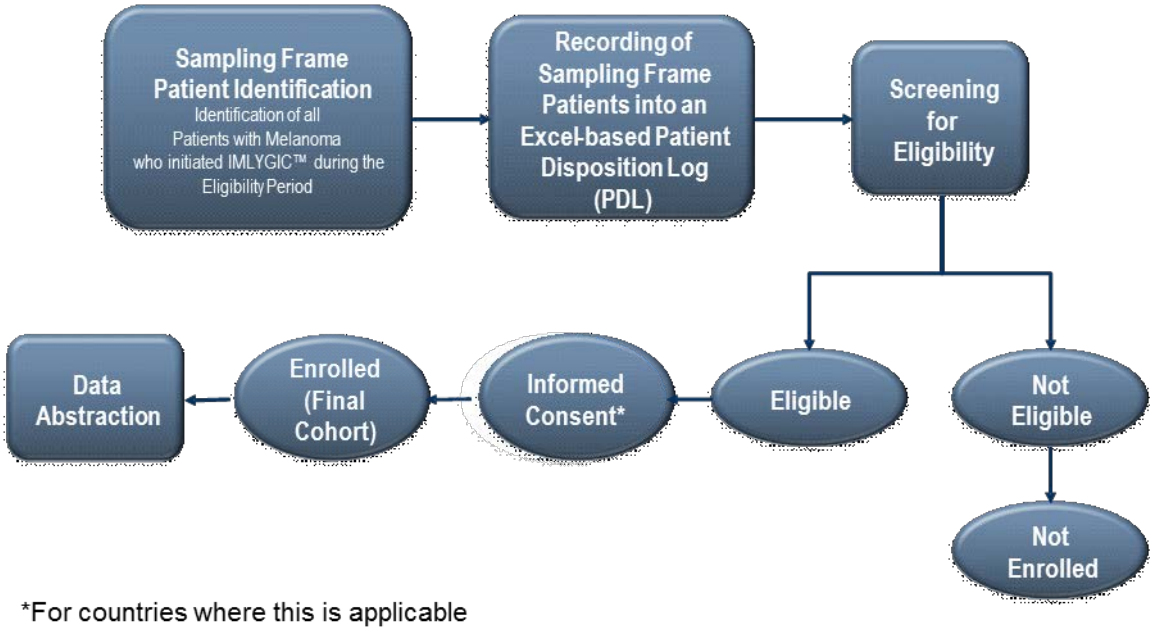
Figure 1. Eligibility and Study Period for Subjects



[a] Examples of Imlygic subject profiles eligible for study inclusion.
[b] Eligible subjects are patients with unresectable Stage IIIB-IVM1a melanoma initiating Imlygic treatment following EMA approval on 17 December 2015 and up to date of site initiation. Retrospective chart abstraction will span from date of primary melanoma diagnosis to date of site initiation. A one-time physician survey will also be conducted at each study site.
[c] Data collection will include: demographics, melanoma history, clinical characteristics, melanoma treatment prior to Imlygic treatment, use of Imlygic treatment, use of other melanoma treatment after Imlygic treatment, concomitant medication, clinical outcomes during and after Imlygic treatment
[d] No data will be collected after date of site initiation

Figure 2. Patient Identification and Enrolment

*For countries where this is applicable.



*For countries where this is applicable

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 PPD 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 **Unresectable Stage IIIB-IVM1a** 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) **with no bone, brain, lung or other visceral disease**. 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 **with** 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 Austria, Germany, **Netherlands,** the United Kingdom (UK), and potentially other European countries. 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. The study population will consist of **unresectable stage IIIB-IVM1a** melanoma patients who received **at least an initial IMLYGIC® dose at a concentration of 10^6 plaque forming units (PFU)/mL and at least one subsequent dose at a concentration of 10^8 PFU/mL**. Data will be collected retrospectively from patient medical charts spanning the date of **primary** 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**-**IVM1a, received **an initial IMLYGIC® dose at a concentration of 10^6 PFU/mL and at least one subsequent dose at a concentration of 10^8 PFU/mL** 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 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.

- 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 **approximately 60** medical chart reviews. **At least one physician from each participating study site, approximately 10 HCPs, will participate in the one-time survey.** 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

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason
1	**25 October 2017**	**See summary of changes**		

6. Milestones

Milestone	Planned date*
Start of data collection	**June 2017**
End of data collection	**June 2018**
Final report of study results	**August/September 2018**

* 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 is 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