EUROPEAN UNION RISK MANAGEMENT PLAN

Imlygic® (Talimogene Laherparepvec)

Marketing Authorization Holder:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	11.1
Date:	19 September 2023
Supersedes:	Version 11.0, dated 26 May 2023

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	11.1
Data lock point of this RMP:	26 October 2022
Date of final sign-off:	19 September 2023
Rationale for submitting an updated RMP:	To remove the important potential risk 'Talimogene Laherparepvec-mediated Anti-GM-CSF Antibody Response'

Summary of significant changes in this RMP:

Part/Module/Annex	Major Change(s)	Version Number and Date
Part II: Safety Specification		
SI: Epidemiology of the Indication(s) and Target Population(s)	Updated epidemiology based on current literature	Version 11.0; 26 May 2023
	Updated 'Main Existing Treatment Options' to present the main treatment information	Version 11.1; 19 September 2023
SIII: Clinical Trial Exposure	Updated clinical trial exposure data with Data Lock Point (DLP) of 26 October 2022	Version 11.0; 26 May 2023
SV: Postauthorization Experience	Updated postauthorization exposure data with DLP of 26 October 2022	Version 11.0; 26 May 2023
SVII: Identified and Potential Risks	Removed the important potential risk of 'Talimogene Laherparepvec-mediated Anti-GM-CSF Antibody Response'	Version 11.0; 26 May 2023
	Updated the Evidence Source of the Missing Information 'Pregnant and Lactating Women' to align with postauthorization exposure data with DLP of 26 October 2022	
SVIII: Summary of the Safety Concerns	Aligned with the changes in Module SVII	Version 11.0; 26 May 2023
Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies)	Aligned with the changes in Module SVII	Version 11.0; 26 May 2023
Part IV: Plans for Postauthorization Efficacy Studies	Removed the following completed Postauthorization Efficacy Study • Study 20110266	Version 11.0; 26 May 2023
	Aligned with the changes in Module SVII	
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	Aligned with the changes in Module SVII	Version 11.0; 26 May 2023

Part/Module/Annex	Major Change(s)	Version Number and Date
Part VI: Summary of the Risk Management Plan	Aligned with the changes in Module SVII	Version 11.0; 26 May 2023
Part VII: Annexes		
Annex 5: Protocols for Proposed and Ongoing Studies in RMP Part IV	Removed the following completed study: Study 20110266	Version 11.0; 26 May 2023
Annex 7: Other Supporting Data (Including Referenced Materials)	Updated references section Removed the following validation summaries related to the removed important potential risk of 'Talimogene Laherparepvec-mediated Anti-GM-CSF Antibody Response': • Validation of a Cell Based Method for the Detection of Neutralizing Antibodies Against Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) in Human Serum • Validation of a Biosensor Immunoassay to Detect Antibodies Against GM-CSF in Human Serum	Version 11.0; 26 May 2023

Other RMP versions under evaluation:	None
Details of the currently approved RMP:	
Version number:	10.2
Approved with procedure:	EMEA/H/C/002771/II/0059
Date of approval (opinion date):	26 April 2023
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
ADR	adverse drug reaction
AIDS	acquired immune deficiency syndrome
ATC Code	Anatomical Therapeutic Chemical Classification System [ATC] Code
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CHMP	Committee for Medicinal Products for Human Use
CNS	central nervous system
CSR	clinical study report
EEA	European Economic Area
EMA	European Medicines Agency
EMR	Electronic Medical Record
EPAR	European Public Assessment Report
EU	European Union
EUR	Europe (European Union, European Economic Area, Switzerland, and the United Kingdom);
GM-CSF	granulocyte macrophage colony stimulating factor
HCP	healthcare provider
HIV	human immunodeficiency virus
HSV	herpes simplex virus
HSV-1	herpes simplex virus type 1
IFN-PKR	interferon protein kinase R
INN	International Nonproprietary Name
IV	intravenous
MAH	marketing authorization holder
MEK	mitogen-activated protein kinase kinase
OSCER	Oncology Services Comprehensive Electronic Record
PBRER	Periodic Benefit Risk Evaluation Report
PEB	Physician Education Booklet
PFU	plaque-forming units
PI	Product Information
PL	package leaflet
PSB	Patient Safety Brochure

Term/Abbreviation	Explanation
PSUR	periodic safety update report
qPCR	quantitative polymerase chain reaction
QPPV	Qualified Person for Pharmacovigilance
QT	interval of ventricular depolarization and subsequent repolarization
QTc	corrected QT interval
RMP	risk management plan
SCID	severe combined immunodeficiency
SmPC	Summary of Product Characteristics
$TCID_{50}$	50% tissue culture infective dose
TVEC	talimogene laherparepvec

PART I. PRODUCT(S) OVERVIEW

Table 1. Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Talimogene laherparepvec
Pharmacotherapeutic group (Anatomical Therapeutic Chemical[ATC] Code)	Antineoplastic and immunomodulating agents; ATC Code L01XX51
Marketing authorization holder (MAH)	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Imlygic®
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Talimogene laherparepvec is an antineoplastic and immunomodulating agent.
Summary of mode of action	Talimogene laherparepvec is an oncolytic immunotherapy that is derived from herpes simplex virus type 1 (HSV-1). Talimogene laherparepvec has been modified to replicate within tumors and to produce the immune stimulatory protein human granulocyte macrophage colony stimulating factor (GM-CSF). Talimogene laherparepvec causes the death of tumor cells and the release of tumor-derived antigens. It is thought that together with GM-CSF, it will promote a systemic anti-tumor immune response and an effector T-cell response. The modifications to talimogene laherparepvec from HSV-1 include deletion of ICP34.5 and ICP47. Whereas anti-viral immune responses defend normal cells following infection by talimogene laherparepvec, tumors have been shown to be susceptible to injury and cell death from ICP34.5-deficient HSV-1 viruses, including talimogene laherparepvec. Deletion of ICP47 prevents down-regulation of antigen presentation molecules and increases the expression of herpes simplex virus (HSV) *US11* gene, thereby enhancing viral replication in tumor cells.
Important information about its composition	Talimogene laherparepvec is produced in Vero cells by recombinant DNA technology.

Table 1. Product Overview

Hyperlink to the Product Information (PI)	https://www.ema.europa.eu/documents/product-information/imlygic-epar-product-information_en.pdf
Indication(s) in the EEA	
Current (if applicable):	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.
Proposed (if applicable):	Not applicable
Dosage in the EEA	
Current (if applicable):	Imlygic is administered by intralesional injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance. The initial recommended dose is up to a maximum of 4 mL of Imlygic at a concentration of 10^6 (1 million) plaque-forming units (PFU)/mL. Subsequent doses should be administered up to 4 mL of Imlygic at a concentration of 10^8 (100 million) PFU/mL. The total injection volume for each treatment visit should be up to a maximum of 4 mL. The second treatment visit should occur 3 weeks following the initial treatment visit, with subsequent visits occurring at a treatment interval of 2 weeks.
Proposed (if applicable):	Not applicable
Pharmaceutical form(s) and strength(s)	
Current (if applicable):	One mL solution in a single use vial (cyclic olefin polymer plastic resin) with stopper (chlorobutyl elastomer) and seal (aluminium) with flip-off cap (polypropylene). Each vial contains 1 mL deliverable volume of Imlygic at a nominal concentration of 1 x 10^6 (1 million) PFU/mL or 1 x 10^8 (100 million) PFU/mL.
Proposed (if applicable):	Not applicable
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

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PART II. SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Table 2. Summary of Epidemiology of Melanoma That is Regionally or Distantly Metastatic

Incidence	The annual global incidence of melanoma in 2020 was about 325 000 new cases and 57 000 deaths (Sung et al, 2021). In Europe (EU-27), the incidence of melanoma is about 106 400 new cases and 16 500 deaths (European Commission, 2023).
Prevalence	The number of prevalent cases of melanoma in Europe was estimated to be 517 196 in 2020 (Ferlay et al, 2020). In 2020, there were an estimated 1 413 976 people living with melanoma of the skin in the United States (US) (SEER, 2023).
Demographics of population in the authorized indication and risk factors for the disease	The highest rates are in Australia and New Zealand (~60 cases per 100 000 inhabitants per year), then the US (~30 cases per 100 000 per year) and Europe (~20 cases per 100 000 per year), and the lowest rates are in Africa and Asia (< 1 case per 100 000 per year) (Schadendorf et al, 2015). As seen in the US, melanoma is more frequent among non-Hispanic White males, with an annual incidence rate (per 100 000) of 37.9 and 25.2 among White men and women, respectively. For comparison, the male and female incidence was 1.0 and 0.9 among non-Hispanic Blacks, and 4.5 and 4.3 among Hispanics based on 2016-2020 age-adjusted rates. The overall median age of melanoma diagnosis is 66, with 67% of diagnoses made in those ages 55 to 84 (SEER, 2023). Factors (Russak and Rigel, 2012) that increase the risk of developing melanoma include: • history of blistering sunburns as a teenager • red or blonde hair • family or personal history of melanoma • history of actinic keratoses • ultraviolet radiation from sun exposure or tanning beds (Boniol et al, 2012; Gandini et al, 2005b) • skin type (Olsen et al, 2010) • autoimmune disease (Singh et al, 2014) • people that are immunocompromised (Olsen et al, 2014) • moles and freckles (Gandini et al, 2005a)

Table 2. Summary of Epidemiology of Melanoma That is Regionally or Distantly Metastatic

Main existing treatment options	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 (*v-raf* murine sarcoma viral oncogene homolog B1 [BRAF] and mitogen-activated protein kinase kinase [MEK] inhibitors) and oncolytic viral therapy. Systemic immunotherapies work to stimulate an individual's immune system to destroy cancer cells more effectively. About 40% to 50% of melanomas have *BRAF* gene mutations and approved targeted therapies include vemurafenib, dabrafenib, trametinib, a combination of dabrafenib plus trametinib, or a combination of encorafenib and binimetinib. Other available treatments for unresectable or metastatic melanoma may include chemotherapy (dacarbazine, temozolomide, or other agents either alone or in combination).
Natural history of the indicated condition in the population, including mortality and morbidity	The global annual number of deaths from melanoma was about 57 000 deaths in 2020 (Sung et al, 2021); Europe (EU-27) in 2020, 16 500 deaths (European Commission, 2023); and the U.S. estimated for 2023, 7 990. In the U.S. the annual death rate from melanoma was 2.1 per 100 000 based on 2016-2020 deaths age-adjusted. The median age at death with melanoma was 72 with 50% of deaths occurring among persons aged 65-84 years. (SEER, 2023). While the overall 5-year survival after diagnosis of melanoma in the US was 93.5%, survival was highly dependent on initial stage: 99.6% for localized (confined to primary site); 73.9% for regional (spread to regional lymph nodes); and 35.1% for distant (metastasis) (SEER, 2023). Detection of 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).

Table 2. Summary of Epidemiology of Melanoma That is Regionally or Distantly Metastatic

Natural history of the indicated condition in the population, including mortality and morbidity (continued)	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 tumor characteristics, such as tumor location (ear, lips, areas of chronic ulcers, or inflammation), clinical size of lesion (> 2 cm in diameter), histological depth extension (beyond subcutaneous tissue), histological type, and degree of differentiation, and immunosuppression (Stratigos et al, 2015). In Europe, 5-year survival rate is on average 83% (Crocetti et al, 2015). However, survival decreases with worsening stage and varies widely. The 5-year survival is estimated to be > 95% for stage 1, 65% to 93% for stage II, 41% to 71% for stage III, and 9% to 28% for stage IV. The 5-year recurrence-free survival is estimated to be between 29% to 44% for stage III (Svedman et al, 2016).
Important comorbidities	The most common comorbidities in the melanoma population (prevalence between 2% to 4%) are (Grann et al, 2013): • Any cancer (excluding skin cancer) • Cerebrovascular disease • Chronic obstructive pulmonary disease • Diabetes mellitus (type I and II) Using data from Danish registries 1987-2009, researchers examined the impact of comorbidities on mortality in patients with melanoma vs a cohort of subjects in the general population matched by age, gender, and prevalent comorbidities. As expected, with increasing level of comorbidities, mortality rates increased in both the melanoma cohort and the matched general population. However, there was a marked interaction with excess risk of mortality in the melanoma cohort with higher levels of comorbidity. A higher prevalence of comorbidity was associated with a more advanced stage of melanoma at diagnosis (Grann et al, 2013).

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Part II: Module SII - Nonclinical Part of the Safety Specification

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings (High-Level Summary)	Relevance to Human Usage
Safety in immune-deficient mice	Talimogene laherparepvec was injected into various xenograft tumors at doses up to 2×10^8 PFU/kg (30-fold over the maximum clinical dose) in immunodeficient mice (nude and severe combined immunodeficiency [SCID]). Lethal systemic viral infection was observed in up to 20% of nude mice (primarily deficient in T lymphocyte function) and 100% of SCID mice (devoid of both T and B lymphocytes). Viral inclusion bodies and/or necrosis in enteric neurons in the gastrointestinal tract, adrenal gland, and skin were observed in both mouse strains; and in pancreatic islet cells, eye, pineal gland, and brain of SCID mice. Across studies, fatal disseminated viral infection was observed in 14% of nude mice following treatment with talimogene laherparepvec at doses that are 10- to 100-fold higher than those that result in 100% lethality with wild-type HSV-1.	Talimogene laherparepvec is contraindicated in patients who are severely immunocompromised (eg, patients with severe congenital or acquired cellular and/or humoral immune deficiency). These patients may be at risk for life-threatening disseminated herpetic infection. Disseminated herpetic infection may also occur in immunocompromised patients (such as those with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), leukemia, lymphoma, common variable immunodeficiency, or who require chronic high-dose steroids or other immunosuppressive agents. Consider the risks and benefits of treatment before administering talimogene laherparepvec to these patients. Accidental exposure may lead to transmission of talimogene laherparepvec and herpetic infection. Healthcare providers (HCPs), close contacts (household members, caregivers, sex partners, or persons sharing the same bed), pregnant women, and neonates should avoid direct contact with injected lesions or body fluids of treated patients. Close contacts who are pregnant or immunocompromised should not change the patient's dressings or clean their injection sites. Disseminated herpetic infection(Table 13) and accidental exposure of HCP to talimogene laherparepvec are included as important identified risks (Table 14).Pregnant and lactating women are included as missing information (Table 20).

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings (High-Level Summary)	Relevance to Human Usage
Reproductive and developmental toxicity	There were no impacts to male or female reproductive tissues following treatment of adult mice at doses up to 4 x 10^8 PFU/kg (60-fold higher, on a PFU/kg basis, compared to the maximum clinical dose). No effects on embryo-fetal development were observed when talimogene laherparepvec was administered during organogenesis to pregnant mice at doses up to 4 x 10^8 (400 million) PFU/kg (60-fold higher, on a PFU/kg basis, compared to the maximum clinical dose). Negligible amounts (< 0.001% of maternal blood levels) of talimogene laherparepvec DNA were found in fetal blood.	If talimogene laherparepvec is used during pregnancy, or if the patient becomes pregnant while taking talimogene laherparepvec, the patient should be apprised of the potential hazards to the fetus and/or neonate. Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with talimogene laherparepvec. If a pregnant woman has an infection with wild-type HSV-1 (primary or reactivation), there is potential for the virus to cross the placental barrier and also a risk of transmission during birth due to viral shedding. Infections with wild-type HSV-1 have been associated with serious adverse effects, including multi-organ failure and death, if a fetus or neonate contracts the wild-type herpes infection. While there are no clinical data to date on talimogene laherparepvec infections in pregnant women, there could be a risk to the fetus or neonate if talimogene laherparepvec were to act in the same manner. Transplacental metastases of malignant melanoma can occur. Because talimogene laherparepvec is modified to enter and replicate in the tumor tissue, there could be a risk of fetal exposure to talimogene laherparepvec from tumor tissue that has crossed the placenta. Accidental exposure may lead to transmission of talimogene laherparepvec and herpetic infection. Healthcare providers, close contacts (household members, caregivers, sex partners, or persons sharing the same bed), pregnant women, and neonates should avoid direct contact with injected lesions or body fluids of treated patients. Close contacts who are pregnant or immunocompromised should not change the patient's dressings or clean their injection sites. It is not known whether talimogene laherparepvec is transferred into human milk. Because medicinal products can be found in human milk, a decision should be made whether to discontinue nursing or to discontinue talimogene laherparepvec while nursing. Accidental exposure of HCP to talimogene laherparepvec is included as an important identified risk (Table 14), and pregnant and lactating women are included as missing information (Table 20).

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings (High-Level Summary)	Relevance to Human Usage
Biodistribution	Following intralesional administration in mice, talimogene laherparepvec DNA was detected in approximately 40% of tumor samples and in ≤ 20% of blood and organ tissue samples (eg, spleen, lymph node, liver, heart, and kidneys). Talimogene laherparepvec DNA was detected in ≤ 2% of samples in brain, ovary, and salivary gland, and was not detected in bone marrow, eyes, shedding tissues (lachrymal glands, nasal mucosa), or feces. The highest concentration of talimogene laherparepvec DNA was found in injected lesions. All other tissues had significantly lower levels of talimogene laherparepvec DNA than detected overall in lesions (< 0.5% of the highest concentration detected in any tumors). Talimogene laherparepvec DNA could be found in injected tumors through 84 days after the last dose, but was cleared from the majority (94%) of blood samples by 7 days after the last dose. Following intravenous administration in mice, talimogene laherparepvec DNA was detected in approximately 8% of peripheral nerve samples.	Accidental exposure may lead to transmission of talimogene laherparepvec and herpetic infection. Healthcare providers, close contacts (household members, caregivers, sex partners, or persons sharing the same bed), pregnant women, and neonates should avoid direct contact with injected lesions or body fluids of treated patients. Accidental needle stick and splash back have been reported in HCPs during preparation and administration of talimogene laherparepvec. In clinical studies, herpetic infections (including cold sores and herpes keratitis) have been reported in patients treated with talimogene laherparepvec. Patients who develop herpetic infections should be advised to follow standard hygienic practices to prevent viral transmission. Accidental exposure of HCP to talimogene laherparepvec is included as an important identified risk (Table 14).

Part II: Module SIII - Clinical Trial Exposure

Table 4. Total Subject Exposure to Talimogene Laherparepvec in Clinical Trials by Indication and Duration Safety Analysis Set

	Exposure to Talimogene Laherparepvec by Duration					
	< 1 year n (subj-yrs)	≥ 1 year n (subj-yrs)	≥ 2 year n (subj-yrs)	≥ 3 year n (subj-yrs)	≥ 4 year n (subj-yrs)	Total n (subj-yrs)
Melanoma (monotherapy)	513 (228.7)	93 (165.5)	24 (71.2)	10 (38.3)	3 (13.4)	606 (394.2)
Melanoma (combination therapy)						
Talimogene laherparepvec + Ipilimumab	95 (43.6)	15 (25.4)	4 (9.8)	0 (0.0)	0 (0.0)	110 (69.0)
Talimogene laherparepvec + Pembrolizumab	331 (126.9)	111 (189.2)	49 (102.2)	0 (0.0)	0 (0.0)	442 (316.1)
Talimogene laherparepvec + Surgery	57 (16.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	57 (16.3)
Head and Neck (combination therapy)						
Talimogene laherparepvec + Cisplatin/RT	19 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (4.2)
Talimogene laherparepvec + Pembrolizumab	34 (9.2)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	36 (11.9)
Other Solid Tumors (monotherapy)	71 (13.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	72 (14.3)
Other Solid Tumors (combination therapy)						
Talimogene laherparepvec + Atezolizumab	31 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	31 (5.6)
Talimogene laherparepvec + Pembrolizumab	89 (23.4)	4 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	93 (29.7)
Pediatrics (Non-CNS Tumors) (monotherapy)	15 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (4.2)
Total	1255 (475.1)	226 (390.4)	77 (183.1)	10 (38.3)	3 (13.4)	1481 (865.5)

n = number of subjects exposed to talimogene laherparepvec; subj-yrs = total subject-yrs of follow-up.
Data as of 26 October 2022.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Program: /userdata/stat/amg678/safety/rmp/analysis/202210/tables/t-expo-01.sas
Output: t14-05-001-001-expo-01-l.rtf (Date Generated: 13APR2023:19:15) Source Data: adsl_rmp

Table 5. Exposure to Talimogene Laherparepvec Clinical Trials by Dose Level and Indication
Safety Analysis Set

	Exposure to Talimogene Laherparepvec by Dose Level							
	10^4 PFU/mL → 10^5 PFU/mL n (subj-yrs)	10^5 PFU/mL only dosing n (subj-yrs)	10^5 PFU/mL → 10^6 PFU/mL n (subj-yrs)	10^6 PFU/mL only dosing n (subj-yrs)	10^6 PFU/mL → 10^7 PFU/mL n (subj-yrs)	10^6 PFU/mL → 10^8 PFU/mL n (subj-yrs)	10^7 PFU/mL only dosing n (subj-yrs)	10^8 PFU/mL only dosing n (subj-yrs)
Melanoma (monotherapy)	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.9)	0 (0.0)	593 (392.8)	0 (0.0)	2 (0.5)
Melanoma (combination therapy)								
Talimogene laherparepvec + Ipilimumab	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	110 (69.0)	0 (0.0)	0 (0.0)
Talimogene laherparepvec + Pembrolizumab	0 (0.0)	0 (0.0)	0 (0.0)	22 (1.9)	2 (0.6)	415 (311.1)	0 (0.0)	2 (2.4)
Talimogene laherparepvec + Surgery	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	56 (16.2)	0 (0.0)	0 (0.0)
Head and Neck (combination therapy)								
Talimogene laherparepvec + Cisplatin/RT	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.1)	4 (0.9)	9 (2.2)	0 (0.0)	0 (0.0)
Talimogene laherparepvec + Pembrolizumab	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.9)	0 (0.0)	25 (11.0)	0 (0.0)	0 (0.0)
Other Solid Tumors (monotherapy)	3 (1.0)	1 (0.1)	3 (0.5)	15 (1.3)	17 (5.8)	21 (4.3)	5 (0.4)	7 (0.9)
Other Solid Tumors (combination therapy)								
Talimogene laherparepvec + Atezolizumab	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.8)	0 (0.0)	22 (4.8)	0 (0.0)	0 (0.0)
Talimogene laherparepvec + Pembrolizumab	0 (0.0)	0 (0.0)	0 (0.0)	13 (1.1)	9 (3.4)	71 (25.2)	0 (0.0)	0 (0.0)
Pediatrics (Non-CNS Tumors) (monotherapy)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	14 (4.2)	0 (0.0)	0 (0.0)
Total	3 (1.0)	1 (0.1)	3 (0.5)	89 (8.2)	32 (10.6)	1336 (840.8)	5 (0.4)	11 (3.8)

n = number of subjects exposed to talimogene laherparepvec; subj-yrs = total subject-yrs of follow-up.
Data as of 26 October 2022.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Subject 26566050357 exposed to TVEC but the information of concentration is missing.
Program: /userdata/stat/amg678/safety/rmp/analysis/202210/tables/t-expo-dose.sas
Output: t14-05-001-004-expo-dose-l.rtf (Date Generated: 13APR2023:19:15) Source Data: adsl_rmp, adexsbj

Table 6. Total Subjects Exposure to Talimogene Laherparepvec in Clinical Trials by Indication, Gender and Age Group
Safety Analysis Set

	Children (eg, 2 to 11 years) n (subj-yrs)	Adolescents (eg, 12 to 17 years) n (subj-yrs)	Adults (eg, 18 to 64 years) n (subj-yrs)	Elderly people (eg, 65 to 74 years) n (subj-yrs)	Elderly people (eg, 75+ years) n (subj-yrs)
Male					
Melanoma (monotherapy)	0 (0.0)	0 (0.0)	148 (88.5)	87 (57.2)	87 (47.8)
Melanoma (combination therapy)					
Talimogene laherparepvec + Ipilimumab	0 (0.0)	0 (0.0)	33 (20.5)	22 (16.9)	12 (7.8)
Talimogene laherparepvec + Pembrolizumab	0 (0.0)	0 (0.0)	133 (93.7)	75 (53.9)	50 (37.5)
Talimogene laherparepvec + Surgery	0 (0.0)	0 (0.0)	16 (4.7)	14 (4.0)	4 (1.0)
Head and Neck (combination therapy)					
Talimogene laherparepvec + Cisplatin/RT	0 (0.0)	0 (0.0)	16 (3.5)	1 (0.3)	0 (0.0)
Talimogene laherparepvec + Pembrolizumab	0 (0.0)	0 (0.0)	16 (6.4)	11 (3.3)	2 (1.1)
Other Solid Tumors (monotherapy)	0 (0.0)	0 (0.0)	23 (4.4)	5 (1.2)	1 (0.2)
Other Solid Tumors (combination therapy)					
Talimogene laherparepvec + Atezolizumab	0 (0.0)	0 (0.0)	7 (1.3)	4 (0.7)	1 (0.3)
Talimogene laherparepvec + Pembrolizumab	0 (0.0)	0 (0.0)	20 (7.6)	17 (7.2)	7 (1.4)
Pediatrics (Non-CNS Tumors) (monotherapy)*	2 (0.6)	6 (1.2)	2 (1.0)	0 (0.0)	0 (0.0)
Total	2 (0.6)	6 (1.2)	414 (231.6)	236 (144.6)	164 (97.2)

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Footnotes and abbreviations are defined on the last page of this table

Table 6. Total Subjects Exposure to Talimogene Laherparepvec in Clinical Trials by Indication, Gender and Age Group
Safety Analysis Set

	Children (eg, 2 to 11 years) n (subj-yrs)	Adolescents (eg, 12 to 17 years) n (subj-yrs)	Adults (eg, 18 to 64 years) n (subj-yrs)	Elderly people (eg, 65 to 74 years) n (subj-yrs)	Elderly people (eg, 75+ years) n (subj-yrs)
Female					
Melanoma (monotherapy)	0 (0.0)	0 (0.0)	152 (107.0)	57 (37.0)	75 (56.7)
Melanoma (combination therapy)					
Talimogene laherparepvec + Ipilimumab	0 (0.0)	0 (0.0)	22 (13.8)	9 (3.3)	12 (6.6)
Talimogene laherparepvec + Pembrolizumab	0 (0.0)	0 (0.0)	96 (73.3)	49 (35.3)	39 (22.4)
Talimogene laherparepvec + Surgery	0 (0.0)	0 (0.0)	12 (3.6)	4 (1.1)	7 (2.0)
Head and Neck (combination therapy)					
Talimogene laherparepvec + Cisplatin/RT	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Talimogene laherparepvec + Pembrolizumab	0 (0.0)	0 (0.0)	5 (0.6)	1 (0.4)	1 (0.1)
Other Solid Tumors (monotherapy)	0 (0.0)	0 (0.0)	34 (6.9)	7 (1.4)	2 (0.2)
Other Solid Tumors (combination therapy)					
Talimogene laherparepvec + Atezolizumab	0 (0.0)	0 (0.0)	14 (2.6)	5 (0.7)	0 (0.0)
Talimogene laherparepvec + Pembrolizumab	0 (0.0)	0 (0.0)	40 (9.8)	6 (2.9)	3 (0.8)
Pediatrics (Non-CNS Tumors) (monotherapy)*	0 (0.0)	4 (0.6)	1 (0.8)	0 (0.0)	0 (0.0)
Total	0 (0.0)	4 (0.6)	377 (218.7)	139 (82.1)	139 (88.8)

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n = number of subjects exposed to talimogene laherparepvec; subj-yrs = total subject-yrs of follow-up.
Data as of 26 October 2022.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
*Study 20110261, evaluating the safety and efficacy of talimogene laherparepvec in pediatric subjects with advanced non-central nervous system tumors that are amenable to direct injection, enrolled pediatric subjects aged 2 to 21 years. Therefore, pediatric subjects 18 to 21 years of age are included among the adult age group of 18 to 64 years.
Program: /userdata/stat/amg678/safety/rmp/analysis/202210/tables/t-expo-02.sas
Output: t14-05-001-002-expo-02-l.rtf (Date Generated: 13APR2023:19:15) Source Data: adsl_rmp

Table 7. Total Subject Exposure to Talimogene Laherparepvec in Clinical Trials by Indication and Race/Ethnic Group
Safety Analysis Set

	Race						Ethnic			
	White n (subj-yrs)	Black or African American n (subj-yrs)	Asian n (subj-yrs)	Other n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)	Hispanic or Latino n (subj-yrs)	Non Hispanic or Latino n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)
Melanoma (monotherapy)	577 (373.6)	2 (0.3)	22 (17.1)	5 (3.2)	0 (0.0)	606 (394.2)	12 (9.3)	593 (384.7)	1 (0.3)	606 (394.2)
Melanoma (combination therapy)										
Talimogene laherparepvec + Ipilimumab	108 (68.2)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	110 (69.0)	1 (0.5)	109 (68.5)	0 (0.0)	110 (69.0)
Talimogene laherparepvec + Pembrolizumab	420 (294.8)	2 (1.1)	7 (10.0)	13 (10.3)	0 (0.0)	442 (316.1)	13 (9.7)	424 (299.7)	5 (6.7)	442 (316.1)
Talimogene laherparepvec + Surgery	54 (15.4)	1 (0.3)	0 (0.0)	2 (0.6)	0 (0.0)	57 (16.3)	3 (0.8)	53 (15.2)	1 (0.3)	57 (16.3)
Head and Neck (combination therapy)										
Talimogene laherparepvec + Cisplatin/RT	18 (4.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	19 (4.2)	0 (0.0)	2 (0.3)	17 (3.9)	19 (4.2)
Talimogene laherparepvec + Pembrolizumab	33 (11.2)	1 (0.1)	1 (0.1)	1 (0.6)	0 (0.0)	36 (11.9)	2 (0.5)	34 (11.5)	0 (0.0)	36 (11.9)
Other Solid Tumors (monotherapy)	34 (7.8)	3 (0.5)	3 (1.1)	2 (0.5)	30 (4.5)	72 (14.3)	2 (0.3)	23 (5.1)	47 (8.9)	72 (14.3)

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Footnotes and abbreviations are defined on the last page of this table

Table 7. Total Subject Exposure to Talimogene Laherparepvec in Clinical Trials by Indication and Race/Ethnic Group
Safety Analysis Set

	Race						Ethnic			
	White n (subj-yrs)	Black or African American n (subj-yrs)	Asian n (subj-yrs)	Other n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)	Hispanic or Latino n (subj-yrs)	Non Hispanic or Latino n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)
Other Solid Tumors (combination therapy)										
Talimogene laherparepvec + Atezolizumab	29 (5.4)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	31 (5.6)	1 (0.1)	30 (5.5)	0 (0.0)	31 (5.6)
Talimogene laherparepvec + Pembrolizumab	76 (24.6)	0 (0.0)	16 (4.9)	1 (0.1)	0 (0.0)	93 (29.7)	6 (1.3)	87 (28.4)	0 (0.0)	93 (29.7)
Pediatrics (Non-CNS Tumors) (monotherapy)	11 (3.4)	0 (0.0)	0 (0.0)	4 (0.8)	0 (0.0)	15 (4.2)	3 (0.5)	11 (3.5)	1 (0.2)	15 (4.2)
Total	1360 (808.5)	11 (2.4)	49 (33.1)	31 (16.9)	30 (4.5)	1481 (865.5)	43 (23.0)	1366 (822.4)	72 (20.2)	1481 (865.5)

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n = number of subjects exposed to talimogene laherparepvec; subj-yrs = total subject-yrs of follow-up.
Data as of 26 October 2022.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Program: /userdata/stat/amg678/safety/rmp/analysis/202210/tables/t-expo-03.sas
Output: t14-05-001-003-expo-03-l.rtf (Date Generated: 13APR2023:19:15) Source Data: adsl_rmp

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Pregnant or breastfeeding females	Adequate and well-controlled studies with talimogene laherparepvec have not been conducted in pregnant women. It is not known whether talimogene laherparepvec is transferred into human milk.	Yes	Not applicable.
Evidence of immune suppression	Talimogene laherparepvec is contraindicated in patients who are severely immunocompromised (eg, patients with severe congenital or acquired cellular and/or humoral immune deficiency).	No	Talimogene laherparepvec is contraindicated in patients who are severely immunocompromised (eg, patients with severe congenital or acquired cellular and/or humoral immune deficiency). These patients may be at risk for life-threatening disseminated herpetic infection.
Clinically active cerebral or bone metastases	Due to the significantly shorter survival of patients with symptomatic brain metastases or bone metastases, the efficacy and safety of talimogene laherparepvec may not be accurately evaluated compared to the general melanoma population regarding exposure and outcomes.	No	This patient population was excluded from clinical studies to enable clearer interpretation of safety and efficacy data, because patients with brain and bone metastases have a particularly poor prognosis and are more likely to discontinue treatment early due to clinical deterioration due to underlying disease.

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Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Clinically active cerebral or bone metastases (continued)			There were 4 subjects in Study 005/05, a, phase 3, multicenter, randomized, open-label study of talimogene laherparepvec monotherapy compared with GM-CSF in subjects with unresected, stage IIIB, IIIC, and IV melanoma, who enrolled with cerebral metastases and other subjects who developed cerebral metastases while on treatment and continued therapy.
Greater than 3 visceral metastases (not including lung metastases or nodal metastases associated with visceral organs), and for patients with ≤ 3 visceral metastases, no lesion > 3 cm	Few patients enrolled into the phase 2 clinical study had large volume visceral disease. For the phase 3 melanoma study, a limitation on the number of visceral metastases (not including lung metastases and nodal metastases associated with visceral organs) was used to exclude patients with large volume visceral disease whose survival time may have been expected to be shorter than the minimum response duration of 6 months that was required for the primary endpoint of the study.	No	This patient population was excluded from clinical studies to enable clearer interpretation of safety and efficacy data, because patients with large volume visceral disease have a particularly poor prognosis and are more likely to discontinue treatment early due to clinical deterioration due to underlying disease.
History of second cancer, unless disease-free for > 5 years	Due to competing risks of death due to other active cancer, the treatment effect of talimogene laherparepvec in metastatic melanoma in this setting would be confounded.	No	The patient population was excluded from clinical studies to enable clearer interpretation of data. The coexistence of another active malignancy is unlikely to predict adverse outcome with talimogene laherparepvec.

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Primary ocular or mucosal melanoma	These subtypes of melanoma are generally more aggressive and much less common than cutaneous melanoma. Ocular and mucosal melanoma are a different disease state as compared with cutaneous melanoma and are not expected to have injectable disease.	No	This patient population was excluded from clinical studies to enable clearer interpretation of data.
Prolongation of QT/QTc interval (interval of ventricular depolarization and subsequent repolarization/ corrected QT interval that is less heart rate dependent) (cardiac impairment)	Patients with baseline prolonged QT/QTc have been associated with increased risk of sudden cardiac death both in the general population as well as with use of certain medications, including some that are used in melanoma. To decrease the risk of confounding causes of death, these subjects were excluded from the phase 3 melanoma study.	No	Insufficient human data exist to justify a contraindication in patients with prolonged QT/QTc intervals. Nonclinical data do not suggest a potential for QT prolongation with HSV-1 viruses.
Open herpetic skin lesions	Open herpetic skin lesions at the site of injection could predispose the subject, and those in close contact with the subject, to infection.	No	In clinical studies, herpetic skin infections have been reported in patients treated with talimogene laherparepvec. The Summary of Product Characteristics (SmPC) includes warnings and precautions regarding herpetic infections. In addition, instructions regarding prevention of viral transmission and management of herpetic infection are provided in the SmPC.

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Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Intermittent or chronic treatment with anti-herpetic drug (eg, acyclovir) other than intermittent topical use	Use of anti-herpetic drugs (other than intermittent topical use) would be expected to decrease efficacy because the product is a modified herpes virus that retains sensitivity to anti-herpetic drugs. As with wild-type HSV-1, talimogene laherparepvec is susceptible to acyclovir and other anti-herpetic drugs.	No	Use of anti-herpetic drugs was an exclusion criterion during the clinical development program due to the possibility of confounding the efficacy results. There are no adverse events that are expected to result from the use of anti-herpetic agents.
Fertile males and females who are unwilling to employ adequate means of contraception	No studies of the effects of talimogene laherparepvec on reproduction and development have been performed in humans. The potential for talimogene laherparepvec to be transferred by semen and its effect on sperm are unknown.	No	No effects on embryo-fetal development have been observed in animal studies. The SmPC states that patients should be apprised of the potential hazards to the fetus and/or neonate. Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with talimogene laherparepvec.

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SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 9. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Three pregnancies were reported in which patients were exposed to talimogene laherparepvec prior to or during pregnancy. These include 1 pregnancy from study sources (maternal exposure) and 2 pregnancies from nonstudy sources (1 maternal exposure and 1 paternal exposure).
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities	
Patients with hepatic impairment	There were 40 cases of subjects with hepatic impairment in the clinical trial program.
Patients with renal impairment	There were 9 cases of subjects with renal impairment in the clinical trial program.
Patients with cardiovascular impairment	There were 67 cases of subjects with cardiovascular impairment in the clinical trial program.
Severely Immunocompromised patients	Not included in the clinical development program. Patients who are severely immunocompromised may be at risk for life-threatening disseminated herpetic infection.
Patients with a disease severity different from inclusion criteria in clinical trials	No data available
Population with relevant different ethnic origin	In clinical studies, the majority of subjects were White (Table 7).
Subpopulations carrying relevant genetic polymorphisms	No data available
Other	Not applicable

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, vials or syringes), and on drug utilization parameters. Worldwide unit sales are recorded monthly by country, and are converted to a monthly estimate of person-count (when feasible) or patient-time using region- and product-specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

Vials administered for initial dose have a strength of 10^6 PFU/mL. At first administration, patients receive up to 4 mL, depending on the number and size of lesions. The number of patients exposed to talimogene laherparepvec was estimated based on the number of initial dose vials shipped.

The cumulative number of patients exposed to talimogene laherparepvec through commercial distribution is shown in Table 10 below.

SV.1.2 Exposure

Table 10. Estimated Number of Patients Exposed to Talimogene Laherparepvec, by Region and Demographic Characteristics in the Postmarketing Setting

	Cumulative Number of New Patients Exposed			
Demographic Characteristics	EUR	US	Other	Total
Overall	1450	5748	10	7208
Sex				
Female	522	2069	4	2595
Male	928	3679	6	4613
Age				
< 65	522	2069	4	2595
≥ 65	928	3679	6	4613
Sex				
Female				
< 65	87	345	1	432
≥ 65	435	1724	3	2162
Male				
< 65	435	1724	3	2162
≥ 65	493	1954	3	2451

EMR = electronic medical record; EUR = Europe (European Union, European Economic Area, Switzerland, and the United Kingdom); OSCER = Oncology Services Comprehensive Electronic Records; Other = countries, not otherwise specified above, where Amgen is the marketing authorization holder; US = United States

Note: Numbers may not add to the total due to rounding.

Age and gender breakdowns are based on patient characteristics in OSCER, a US EMR database. Applying these distributions to regions outside the United States requires strong assumptions that are not easily testable.

Cumulative through 26 October 2022

Table 11. Estimated Number of Patient-years of Exposure to Talimogene Laherparepvec, by Region and Demographic Characteristics in the Postmarketing Setting

	Cumulative Number of Patient-years of Exposure			
Demographic Characteristics	EUR	US	Other	Total
Overall	519	1403	2	1924
Sex				
Female	187	505	1	693
Male	332	898	1	1232
Age				
< 65	187	505	1	693
≥ 65	332	898	1	1232
Sex				
Female				
< 65	31	84	0	115
≥ 65	156	421	0	577
Male				
< 65	156	421	0	577
≥ 65	177	477	1	654

EMR = electronic medical record; EUR = Europe (European Union, European Economic Area, Switzerland, and the United Kingdom); OSCER = Oncology Services Comprehensive Electronic Records; Other = countries, not otherwise specified above, where Amgen is the marketing authorization holder; US = United States

Note: Numbers may not add to the total due to rounding.

Age and gender breakdowns are based on patient characteristics in OSCER, a US EMR database. Applying these distributions to regions outside the United States requires strong assumptions that are not easily testable.

Cumulative through 26 October 2022

Postauthorization Use From Business Partners

No business partners have distributed talimogene laherparepvec.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Table 12. New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Removal of Safety Concerns From RMP		
Important Potential Risk: Talimogene Laherparepvec-mediated Anti-GM-CSF Antibody Response:	This important potential risk 'Talimogene Laherparepvec-mediated Anti-GM-CSF Antibody Response' has been removed.	The potential risk of talimogene laherparepvec mediated anti-GM-CSF antibody response was based on the theoretical concerns that viral expression of GM-CSF transgene could lead to the production of GM-CSF and development of anti-GM-CSF antibody response in patients treated with talimogene laherparepvec, and was assumed that it might have a potential impact on the risk-benefit balance of the product. The potential for anti-GM-CSF antibody development was not evaluated in animal studies. Literature review did not reveal any report of anti-GM-CSF antibody response in patients who were administered talimogene laherparepvec. We have found no evidence that adverse events related to the potential risk of developing anti-GM-CSF antibody response have been reported in patients treated with talimogene laherparepvec. No samples were tested for anti GM CSF antibody as no adverse events were reported suggestive of anti GM CSF antibody response in patients treated with talimogene laherparepvec.

GM-CSF = granulocyte macrophage colony stimulating factor; RMP = Risk Management Plan

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 13. Important Identified Risk: Disseminated Herpetic Infection

Potential mechanisms	Talimogene laherparepvec is derived from HSV-1 genetic structure. Tumor-selective viral replication of talimogene laherparepvec is mediated by removal of the ICP34.5 gene, which impairs viral replication in normal cells that have an intact antiviral response driven by the interferon protein kinase R (IFN-PKR) response. When the antiviral response is disrupted in normal cells that are infected with talimogene laherparepvec, viral replication could occur. Additionally, the extent of leaky vasculature within different individual tumors may impact how much talimogene laherparepvec is able to enter the circulation and potentially seed normal tissue at un-injected, distant site.
Evidence source(s) and strength of evidence	This important identified risk was identified based on clinical and postmarketing data.
Characterization of the risk	
Frequency	As of the data cutoff date of 10 March 2022, the frequency of suspected herpetic infections was 114 of 1481 subjects (7.70%) in the talimogene laherparepvec clinical setting, and the reporting rate of suspected herpectic infection was 66 of 6308 patients (1.05%) in the postmarketing setting. Among all subjects who had either suspected disseminated or both localized and disseminated herpetic infection, 1 non-immunocompromised and 1 immunocompromised subject tested positive for TVEC DNA in the clinical setting, and 1 patient with unknown immune status and 2 immunocompromised patients tested positive for TVEC DNA in the postmarketing setting. The frequency of suspected disseminated herpetic infections was 62 of 1481 subjects (4.19%) in the talimogene laherparepvec clinical setting and the reporting rate was 27 of 6308 subjects (0.43%) in the postmarketing setting.
Severity	In clinical trial setting, the majority of events were grade 1 or 2, and no fatal events were reported. In the postmarketing setting, severity was reported for only two events (both grade 2). Thirty-four (34) percent of the events were serious and 66% were non serious. Two fatal cases were reported (talimogene laherparepvec DNA testing was performed in only 1 case; the result was positive and the patient was immunocompromised).
Reversibility	In general, herpetic infections are reversible. Treatment with antiviral therapy, including acyclovir, may be required. Disseminated herpetic infections may require IV antiviral therapy, including acyclovir.
Long-term outcomes	No data are available.

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Footnotes are defined on last page of the table

Table 13. Important Identified Risk: Disseminated Herpetic Infection

Impact on quality of life	Serious cases of disseminated herpetic infection may require hospitalization and treatment with acyclovir or similar antiviral medication. Cases of wild-type herpes simplex dissemination in immunocompromised individuals leading to fulminant multi-organ failure and death are described in the literature. The potential for talimogene laherparepvec to replicate in normal tissues is expected to be attenuated compared to the effects of wild-type HSV-1 in immune competent individuals; however, based on data in animals, disseminated infection and death could occur in severely immunocompromised patients.
Risk groups or risk factors	Immunocompromised individuals are at increased risk. Immunosuppression can be due to congenital immunodeficiency, acquired disease (HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, generalized malignancy), pharmacotherapy (immunosuppressive agents, radiation, or large amounts of corticosteroids), or extremes of age (neonates and elderly) (Chinen and Shearer, 2010; Notarangelo, 2010). The precise risk factors applicable to this risk with talimogene laherparepvec are unknown.
Preventability	The SmPC states to consider the potential risks and potential benefits of treatment with talimogene laherparepvec before administering to patients, with extra caution for immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency or those who require chronic, high dose steroids or other immunosuppressive agents). The SmPC also states that talimogene laherparepvec is contraindicated in patients who are severely immunocompromised. Clinical judgment will be required to determine which patients should be excluded from treatment. The SmPC states that patients who develop herpetic infections should be advised to follow standard hygienic practices to prevent viral transmission.
Impact on the risk-benefit balance of the product	The risk of disseminated herpetic infection has been considered in the benefit-risk assessment and the overall benefit-risk balance is considered to be positive. The impact of this risk can be minimized through product labeling, managed distribution program, Physician Education Booklet, patient safety brochure, and patient alert card.
Public health impact	This patient population is carefully monitored and due to the relatively small number of patients exposed to the drug, the number of patients per year that would be expected to experience the events would not represent a substantial public health issue. Additionally, the contraindication of talimogene laherparepvec in patients who are severely immunocompromised (eg, patients with severe congenital or acquired cellular and/or humoral immune deficiency) should reduce the potential public health impact in this subset of patients.

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AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1; IFN-PKR = interferon protein kinase R; IV = intravenous; SmPC = Summary of Product Characteristics; TVEC = talimogene laherparepvec

Table 14. Important Identified Risk: Accidental Exposure of HCP to Talimogene Laherparepvec

Potential mechanisms	A needle stick injury, spill, or splash back during administration may result in accidental exposure of healthcare workers to talimogene laherparepvec.
Evidence source(s) and strength of evidence	This risk was identified based on reports in the clinical study setting.
Characterization of the risk	
Frequency	Frequency was not calculated. The Virus Surveillance Program (data cutoff date of 30 April 2013) was conducted to quantify potential transmission of talimogene laherparepvec to HCPs from subjects in the phase 3 melanoma clinical study using Healthcare Staff Questionnaires. Healthcare Staff Questionnaires were received from 36 study centers. Five questionnaires reported that study staff exhibited signs or symptoms which may be related to exposure to talimogene laherparepvec. Two reports involved accidental needle sticks. The other questionnaires detailed a case of shingles which was considered unrelated by the medical monitor and principal investigator, a case of herpes on the nares experienced by a coordinator, and a case of a clinical research coordinator with a history of oral herpes who reported a possible exposure (details not provided). Unintended exposure to talimogene laherparepvec among HCPs was also reported for 2 HCPs in Study 20120324, a phase 2, single-arm trial evaluating the biodistribution and shedding of talimogene laherparepvec in subjects with unresected melanoma (stage IIIB to IVM1c). Suspected herpetic event of oral herpes following a needle stick was reported for 1 HCP with a medical history of oral herpes. The results of quantitative polymerase chain reaction (qPCR) testing was negative for talimogene laherparepvec DNA. Unintended exposure subsequent to splash back/direct contact with talimogene laherparepvec to unprotected skin/mucosa was also reported for 1 HCP. No signs/symptoms of suspected herpetic origin were reported; no qPCR testing was done.
Severity	Not well characterized. The severity of herpetic infection due to accidental exposure of HCPs to talimogene laherparepvec is expected to be less than with wild-type HSV-1.
Reversibility	Not applicable.
Long-term outcomes	No data are available.

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Footnotes, including abbreviations, are defined on last page of this table.

Table 14. Important Identified Risk: Accidental Exposure of HCP to Talimogene Laherparepvec

Characterization of the risk (continued)	
Impact on quality of life	Accidental exposure of HCPs to talimogene laherparepvec could result in symptoms of herpetic infection. The incidence and severity of such infection are expected to be less than with wild-type HSV-1; however, they are not well characterized. Whether latency and reactivation may occur is also unknown, although the potential for persistent clinical symptoms is expected to be lower than with wild-type HSV-1.
Risk groups or risk factors	Numerous factors, some modifiable and some not, place HCPs at an increased risk for accidental exposure such as sustaining a needle stick injury. These factors include occupation, training, proper disposal of sharps, and medical activity being performed (National Institute for Occupational Safety and Health, DHHS (NIOSH), 1999; Publication No. 2000-2108).
Preventability	Accidental exposure of HCPs can be minimized by observing safety precautions, communicated in product labeling, to avoid direct contact with talimogene laherparepvec.
Impact on the risk-benefit balance of the product	This risk of accidental exposure of HCP to talimogene laherparepvec has been considered in the benefit-risk assessment and the overall benefit-risk balance is considered to be positive. The impact of this risk can be minimized through product labeling, instructions for use, managed distribution program, and Physician Education Booklet.
Public health impact	The impact on public health is low due to expected low incidence of exposed HCP and consequences. Most adults have had prior exposure to HSV-1 viruses and have pre-existing antibodies. In immune competent individuals who have pre-existing antibodies, infection would be less likely to lead to serious clinical consequences or to lead to repeated clinical episodes. Person-to-person transmission could potentially occur from HCPs who have developed a herpetic infection through accidental exposure to talimogene laherparepvec.

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HCP = healthcare provider; HSV-1 = herpes simplex virus type 1; qPCR = quantitative polymerase chain reaction

Table 15. Important Identified Risk: Immune-mediated Adverse Reactions

Potential mechanisms	Nonclinical and clinical data demonstrate that infection of animals and humans with talimogene laherparepvec is generally associated with characteristic features of a normal host antiviral response. In addition, talimogene laherparepvec is designed to both lyse tumor cells and promote an adaptive anti-tumor response mediated in part through expression of human GM-CSF. It is plausible that immune activation in response to viral infection or secondary to tumor cell destruction/GM-CSF expression could exacerbate underlying (patient-specific) immune conditions.
Evidence source(s) and strength of evidence	This is considered an important identified risk based on reports in the clinical study setting.
Characterization of the risk	
Frequency	The subject incidence of immune-mediated adverse reactions, excluding vitiligo, using an Amgen-defined search strategy was 1.7% (n = 5) in the talimogene laherparepvec group and 0.8% (n = 1) in the GM-CSF group. The between-arm exposure-adjusted adverse event rate difference was 0.01 (95% CI: -0.04, 0.06). The exposure-adjusted subject incidence was 2.9 per 100 subject-years in the talimogene laherparepvec group and 2.1 per 100 subject-years in the GM-CSF group. The subject incidence of vitiligo was 5.1% (n = 15) in the talimogene laherparepvec group.
Severity	Most cases were grade 2 or 3. One grade 4 case was reported, which resolved with treatment, and no fatal cases were reported.
Reversibility	Immune-mediated events may be reversible following treatment with corticosteroids. For some events, talimogene laherparepvec treatment interruption or discontinuation may be required for reversibility.
Long-term outcomes	Immune-mediated events can potentially be life-threatening or fatal.
Impact on quality of life	Hospitalization and/or medication may be required.
Risk groups or risk factors	Risk factors for an immune-mediated adverse reaction include host factors (eg, demographics, other comorbidities), host genotypes (Thong and Tan, *Br J Clin Pharmacol,* 2011; 71:684-700), and pre-existing autoimmune disease.
Preventability	Consider the risks and benefits of talimogene laherparepvec before initiating treatment in patients who have underlying autoimmune disease or before continuing treatment in patients who develop immune-mediated events.
Impact on the risk-benefit balance of the product	This risk of immune-related adverse reactions has been considered in the benefit-risk assessment, and the overall benefit-risk balance remains positive. The impact of this risk can be minimized through product labeling.
Public health impact	Because the nature of immune-mediated adverse reactions varies, the potential public health impact for this risk is difficult to determine.

GM-CSF = granulocyte macrophage colony stimulating factor

Table 16. Important Potential Risk: Transmission of Talimogene Laherparepvec From Patient to Close Contacts or HCPs via Direct Contact With Injected Lesions or Body Fluids Resulting in Symptomatic Infection (Primary or Reactivation)

Potential mechanisms	Talimogene laherparepvec is an attenuated replication competent HSV-1 virus. Thus, exposure to patient secretions/excretions containing live virus could lead to secondary transmission and infection. Herpes simplex virus type 1 strains deficient in the ICP34.5 gene are unable to replicate efficiently in non-tumor cells.
Evidence source(s) and strength of evidence	This risk is considered an important potential risk based on clinical and nonclinical data.
Characterization of the risk	
Frequency	Frequency was not calculated. The Virus Surveillance Program (data cutoff date of 30 April 2013) was conducted to quantify potential transmission of talimogene laherparepvec to close contacts and HCPs from subjects in the phase 3 melanoma clinical study using Family Surveillance Questionnaires and Healthcare Staff Questionnaires. Family Surveillance Questionnaires were received from 177 subjects. Four individuals were reported as having HSV-1 type symptoms, such as cold sores, mouth ulcers and fever blisters. Nonspecific symptoms (eg, rash, sore throat, fever, weakness, hunger) were reported for 7 others. Healthcare Staff Questionnaires were received from 36 study centers. Five questionnaires reported that study staff exhibited signs or symptoms which may be related to exposure to talimogene laherparepvec. Two reports involved accidental needle sticks (Table 14). The other questionnaires detailed a case of shingles which was considered unrelated by the medical monitor and principal investigator, a case of herpes on the nares experienced by a coordinator, and a case of a clinical research coordinator with a history of oral herpes who reported a possible exposure (details not provided). Unintended exposure to talimogene laherparepvec was also reported for 3 close contacts and 2 HCPs in the phase 2 biodistribution and shedding study of talimogene laherparepvec in melanoma (Study 20120324). Suspected herpetic events were reported among 4 cases, including 2 close contacts and 1 HCP with reported oral herpes and medical history of oral herpes. The results of qPCR testing for talimogene laherparepvec DNA were negative for 3 cases providing information regarding tested lesions.
Severity	Not well characterized. The severity of symptomatic herpetic infection due to the transmission of talimogene laherparepvec to close contacts or HCPs is expected to be less than with wild-type HSV-1.
Reversibility	Not applicable.

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Footnotes, including abbreviations, are defined on last page of this table

Table 16. Important Potential Risk: Transmission of Talimogene Laherparepvec From Patient to Close Contacts or HCPs via Direct Contact With Injected Lesions or Body Fluids Resulting in Symptomatic Infection (Primary or Reactivation)

Characterization of the risk (continued)	
Long-term outcomes	There is the potential of developing a HSV infection due to possible latency and reactivation that may occur at a later date.
Impact on quality of life	Minimal impact on affected immunocompetent individuals may be expected based on the reduced potential for replication in healthy tissues. However, the impact is unknown. Individuals with pre-existing antibodies to wild-type HSV-1 may have less significant symptoms. Talimogene laherparepvec is sensitive to acyclovir and other similar antiviral agents, which may be used if clinically warranted.
Risk groups or risk factors	Direct contact with injected lesions, protective dressings, or body fluids of treated patients. The likelihood of transfer of talimogene laherparepvec to a close contact or HCP increases if the contact has a break in the skin or mucous membranes.
Preventability	Transmission of talimogene laherparepvec to close contacts or HCPs can be minimized by observing safety precautions to avoid direct contact with talimogene laherparepvec, injected lesions, protective dressings, and body fluids of treated patients, as communicated in product labeling.
Impact on the risk-benefit balance of the product	This risk of transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) has been considered in the benefit-risk assessment and the overall benefit-risk balance is considered to be positive. The impact of this risk can be minimized through product labeling, instructions for use, managed distribution program, Physician Education Booklet, patient safety brochure, and patient alert card.
Public health impact	The public health impact is unknown as no cases of confirmed transmission of talimogene laherparepvec to close contacts or HCPs have been reported from clinical studies to date.

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HCP = healthcare provider; HSV = herpes simplex virus; HSV-1 = herpes simplex virus type 1; qPCR = quantitative polymerase chain reaction

Table 17. Important Potential Risk: Symptomatic Herpetic Infection Due to Latency and Reactivation of Talimogene Laherparepvec or Wild-type HSV-1 in Patients

Potential mechanisms	The genetic modifications made to talimogene laherparepvec do not prevent the virus from entering latency or subsequently reactivating. However, HSV-1 strains deficient in the ICP34.5 gene are unable to replicate efficiently in non-tumor cells, including neurons, and are impaired for establishment and reactivation from latency when compared to wild-type HSV-1 (Perng et al, 1996; Perng et al, 1995; Spivack et al, 1995; Robertson et al, 1992; Chou et al, 1990). Animal models to evaluate latency/spontaneous reactivation of HSV-1 are not available. At present, there is a poor understanding of the underlying mechanisms through which HSV-1 establishes latency and how, at some time in the future, the lytic program becomes activated in the one or two latently infected neurons which characterize a reactivation event (Thompson et al, 2009).
Evidence source(s) and strength of evidence	This risk is considered an important potential risk based on nonclinical data.
Characterization of the risk	
Frequency	In the phase 3 melanoma clinical study, the subject incidence of adverse events in the HSV infections category was 5.5% (n = 16) of subjects in the talimogene laherparepvec group and 1.6% (n = 2) in the GM-CSF group. The between-group exposure-adjusted adverse event rate difference was 0.05 (95% CI: -0.02, 0.13). The exposure-adjusted subject incidence was 9.5 per 100 subject-years in the talimogene laherparepvec group and 4.1 per 100 subject-years in the GM-CSF group. This frequency represents the subject incidence of adverse events in the HSV infections category (narrow scope); the incidence of symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients is unknown, but may be anticipated to be less than that with wild--type HSV-1 due to the genetic modifications made to talimogene laherparepvec. Whether the reported lesions were due to wild-type herpes or to talimogene laherparepvec could not be confirmed as viral testing was not performed in this study. In the phase 2 biodistribution and shedding study in melanoma (Study 20120324), among 60 subjects receiving at least 1 dose of talimogene laherparepvec, the subject incidence of adverse events suggestive of HSV infection was 8.3% (n = 5). Among 19 subjects with swabs taken from lesions of suspected herpetic origin, 3 subjects (16.7%) had detectable talimogene laherparepvec DNA by qPCR analysis at any time during treatment. No samples from lesions of suspected herpetic origin had detectable talimogene laherparepvec viral activity by $TCID_{50}$ assay.

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Footnotes, including abbreviations, are defined on last page of this table

Table 17. Important Potential Risk: Symptomatic Herpetic Infection Due to Latency and Reactivation of Talimogene Laherparepvec or Wild-type HSV-1 in Patients

Characterization of the risk (continued)		
	Severity	In the phase 3 melanoma clinical study, all adverse events in the HSV infections category had a worst severity of grade 1 (mild) or 2 (moderate). In the phase 2 biodistribution and shedding study in melanoma (Study 20120324), adverse events suggestive of HSV infection were reported with worst grade severity of grade 1 (mild).
	Reversibility	No data are available.
	Long-term outcomes	No data are available.
	Impact on quality of life	The potential impact of herpes infection in individual patients is unknown. Although the potential for talimogene laherparepvec to replicate in healthy tissue is expected to be limited, the most likely manifestation would be cold sores. Most adults have had prior exposure to HSV-1 viruses and have pre-existing antibodies. In immune competent individuals who have pre-existing antibodies, infection would be less likely to lead to serious clinical consequences or to lead to repeated clinical episodes. More extensive herpetic manifestations could have significant impact on the individual. Talimogene laherparepvec is sensitive to acyclovir and other similar antiviral agents.
Risk groups or risk factors		Previous infection with wild-type HSV-1. Fever, stress, and other factors are common triggers of recurrence.
Preventability		This risk can be minimized by preventing primary HSV-1 infection and avoiding common triggers of recurrence.
Impact on the risk-benefit balance of the product		This risk of symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients has been considered in the benefit-risk assessment and the overall benefit-risk balance is considered to be positive. The impact of this risk can be minimized through product labeling, instructions for use, managed distribution program, Physician Education Booklet, patient safety brochure, and patient alert card.
Public health impact		The public health impact is unknown as no cases of symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients have been reported from clinical studies to date.

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GM-CSF = granulocyte macrophage colony stimulating factor; HSV = herpes simplex virus; HSV-1 = herpes simplex virus type 1; qPCR = quantitative polymerase chain reaction; $TCID_{50}$ = 50% tissue culture infective dose

Table 18. Important Potential Risk: Immunocompromised Patients Treated With Talimogene Laherparepvec and Suffering From Concomitant Infection

Potential mechanisms	Based on data in animals treated with talimogene laherparepvec and on clinical data with wild-type HSV-1, disseminated infections are more likely to occur in immunocompromised individuals.
Evidence source(s) and strength of evidence	This important potential risk was identified based on theoretical concern and limited data with immunocompromised patients treated with talimogene laherparepvec.
Characterization of the risk	
Frequency	This event has not been reported in clinical trials.
Severity	Not applicable.
Reversibility	No data are available.
Long-term outcomes	No data are available.
Impact on quality of life	No data are available.
Risk groups or risk factors	Immunosuppression can be due to congenital immunodeficiency, acquired disease (HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, generalized malignancy), pharmacotherapy (immunosuppressive agents, radiation or large amounts of corticosteroids), or extremes of age (neonates and elderly) (Chinen and Shearer, *J Allergy Clin Immunol*, 2010; 125(suppl 2):195-203; Notarangelo, *J Allergy Clin Immunol*, 2010; 125(suppl 2):182-194). The precise risk factors applicable to this risk with talimogene laherparepvec are unknown.
Preventability	The SmPC includes language to consider the potential risks and potential benefits of treatment with talimogene laherparepvec before administering to immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency or those who require chronic, high-dose steroids or other immunosuppressive agents). The SmPC also includes a contraindication in patients who are severely immunocompromised.
Impact on the risk-benefit balance of the product	This risk of immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection has been considered in the benefit-risk assessment and the overall benefit-risk balance is considered to be positive. The impact of this risk can be minimized through product labeling, instructions for use, managed distribution program, and Physician Education Booklet.
Public health impact	The public health impact is unknown as no cases of immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection have been reported from clinical studies to date.

AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1; SmPC = Summary of Product Characteristics

Table 19. Important Potential Risk: Combination With Other Therapies Like Chemotherapy or Immunosuppressive Agents

Potential mechanisms	Combination therapy with chemotherapy or immunosuppressive agents may increase the risk of herpetic infection, including disseminated herpetic infection.
Evidence source(s) and strength of evidence	This is considered an important potential risk based on nonclinical data from immunocompromised mice.
Characterization of the risk	
Frequency	Frequency was not calculated. Clinical Study 004/04, an exploratory study of the safety and biological activity of talimogene laherparepvec in combination with standard concomitant chemoradiotherapy with cisplatin (100 mg/m^2) in the treatment of locally advanced head and neck cancer, enrolled 17 patients. Talimogene laherparepvec in combination with chemoradiotherapy was well tolerated when administered intratumorally to subjects with squamous cell cancer of the head and neck in repeated doses of up to 10^8 PFU/mL. One subject with a previous history of herpes labialis reported a grade 1 adverse event of herpes labialis considered possibly related to investigational product after the second dose of talimogene laherparepvec, which subsequently resolved. Treatment with talimogene laherparepvec did not result in additional toxicities above that normally observed with chemoradiation in this patient population. No deaths or withdrawals due to adverse events occurred during the study.
Severity	Not well characterized.
Reversibility	Not applicable.
Long-term outcomes	No data are available.
Impact on quality of life	The impact on individual patients is unknown.
Risk factors and risk groups	Patients receiving concomitant chemotherapeutic or immunosuppressive therapies.
Preventability	The SmPC includes language to consider the risks and benefits of treatment before administering talimogene laherparepvec to patients who require immunosuppressive agents.
Impact on the risk-benefit balance of the product	The potential risk of combination with other therapies like chemotherapy or immunosuppressive agents has been considered in the benefit-risk assessment and the overall benefit-risk balance is considered to be positive. The impact of this risk can be minimized through product labeling.
Public health impact	The public health impact is expected to be low in individuals treated with talimogene laherparepvec in combination with chemotherapy or immunosuppressive agents based on the reduced potential for replication of talimogene laherparepvec in non-tumor tissue. In addition, talimogene laherparepvec is sensitive to acyclovir and other similar antiviral agents, which may be used if clinically warranted.

PFU = plaque-forming units; SmPC = Summary of Product Characteristics

SVII.3.2 Presentation of the Missing Information

Table 20. Missing Information: Pregnant and Lactating Women

Evidence source	Three pregnancies were reported in which patients were exposed to talimogene laherparepvec prior to or during pregnancy. These include 1 pregnancy from study sources (maternal exposure) and 2 pregnancies from nonstudy sources (1 maternal exposure and 1 paternal exposure).
Population in need of further characterization	No effects on embryo fetal development were observed when talimogene laherparepvec was administered during organogenesis to pregnant mice at doses up to 4 x 10^8 (400 million) PFU/kg (60-fold higher, on a PFU/kg basis, compared to the maximum clinical dose). Negligible amounts (< 0.001% of maternal blood levels) of talimogene laherparepvec DNA were found in fetal blood. If a pregnant woman has an infection with wild-type HSV-1 (primary or reactivation), there is potential for the virus to cross the placental barrier and also a risk of transmission during birth due to viral shedding. Infections with wild-type HSV-1 have been associated with serious adverse effects, including multi organ failure and death, if a fetus or neonate contracts the wild-type herpes infection. While there are no clinical data to date on talimogene laherparepvec infections in pregnant women, there could be a risk to the fetus or neonate if talimogene laherparepvec were to act in the same manner. Transplacental metastases of malignant melanoma can occur (Alexander et al, 2003). Because talimogene laherparepvec is modified to enter and replicate in the tumor tissue, there could be a risk of fetal exposure to talimogene laherparepvec from tumor tissue that has crossed the placenta. Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with talimogene laherparepvec. It is not known whether talimogene laherparepvec is transferred into human milk. Because medicinal products can be found in human milk, a decision should be made whether to discontinue nursing or to discontinue talimogene laherparepvec while nursing.

HSV-1 = herpes simplex virus type 1; PFU = plaque-forming units

Table 21. Missing Information: Pediatric Patients

Evidence source	Children were excluded from talimogene laherparepvec clinical studies; therefore, no information exists on the safety and efficacy of the product in pediatric patients.
Population in need of further characterization	The pharmacokinetic profile of talimogene laherparepvec has not been evaluated in pediatric subjects.

Table 22. Missing Information: Long-term Safety Data

Evidence source	In clinical studies in subjects with melanoma, 1040 subjects received talimogene laherparepvec for < 1 year, 134 subjects for ≥ 1 year, 22 subjects for ≥ 2 years, and 2 subjects for ≥ 3 years. Available data have not identified any new safety concerns of longer treatment with talimogene laherparepvec.
Population in need of further characterization	Study 20130193, a long-term observational study of talimogene laherparepvec to characterize the risk of herpetic infection among patients, close contacts, and health care providers and long term safety in treated patients is ongoing.

Table 23. Missing Information: Long-term Efficacy Data

Evidence source	In clinical studies in subjects with melanoma, 1040 subjects received talimogene laherparepvec for < 1 year, 134 subjects for ≥ 1 year, 22 subjects for ≥ 2 years, and 2 subjects for ≥ 3 year. Available data have not identified any new efficacy concerns of longer treatment with talimogene laherparepvec.
Population in need of further characterization	Long-term efficacy data for patients with melanoma, receiving talimogene laherparepvec, has not been characterized.

Table 24. Missing Information: Treatment of Patients With Metastatic Lesions Greater Than 3 cm

Evidence source	Subjects with metastatic lesions greater than 3 cm were excluded from talimogene laherparepvec clinical studies due to efficacy reasons.
Population in need of further characterization	The indication for talimogene laherparepvec is not limited with regard to the tumor or metastatic lesion size. Therefore, talimogene laherparepvec is likely to be used also in patients with metastatic lesions greater than 3 cm, which could be responsible for a different frequency or pattern of adverse reactions.

Part II: Module SVIII - Summary of the Safety Concerns

Table 25. Summary of Safety Concerns

Important identified risks	• Disseminated herpetic infection • Accidental exposure of HCP to talimogene laherparepvec • Immune-mediated adverse reactions
Important potential risks	• Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients • Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection • Combination with other therapies like chemotherapy or immunosuppressive agents
Missing information	• Pregnant and lactating women • Pediatric patients • Long-term safety data • Long-term efficacy data • Treatment of patients with metastatic lesions greater than 3 cm

AIDS = acquired immune deficiency syndrome; GM-CSF = granulocyte macrophage colony stimulating factor; HCP = healthcare provider; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 26.

Table 26. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Report of Suspected IMLYGIC (Talimogene Laherparepvec) or Herpes Virus Associated Adverse Event	• Disseminated herpetic infection • Accidental exposure of HCP to talimogene laherparepvec • Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients	Monitor clinical trial and postmarketing reports of any suspected herpetic infection in patients or in close contacts or HCPs who have been exposed to the product
Clinical Trial or Postmarket Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact	• Disseminated herpetic infection • Accidental exposure of HCP to talimogene laherparepvec • Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation)	Monitor clinical trial and postmarketing reports of any suspected herpetic infection in close contacts and HCPs who have been exposed to the product

Table 26. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Report of Suspected IMLYGIC (Talimogene Laherparepvec) Autoimmune Adverse Event	Immune-mediated adverse reactions	Monitor clinical trial and postmarketing reports of any immune-mediated events in patients who have been exposed to the product
Pregnancy and lactation follow-up forms	Pregnant and lactating women	Monitor the use of talimogene laherparepvec and potential adverse effects in pregnant and lactating women in the clinical trial and postmarketing settings

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III.2 Additional Pharmacovigilance Activities

Table 27. Category 1 to 3 Postauthorization Safety Studies

Study Short Name, Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
Study 20130193 A postmarketing prospective cohort study of melanoma patients treated with IMLYGIC® (talimogene laherparepvec) in clinical practice to characterize the risk of herpetic infection among patients, close contacts, and health care providers; and long-term safety in treated patients. Category 3	<u>Primary Objective</u> • Estimate the incidence rate of herpetic infection detection of talimogene laherparepvec DNA among patients for up to 5 years after the first IMLYGIC dose. <u>Safety concerns addressed:</u> • Disseminated herpetic infection • Accidental exposure of HCP to talimogene laherparepvec • Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients • Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection • Long-term safety data • Long-term efficacy data	Postmarketing prospective cohort study	Patients with melanoma who received IMLYGIC	Annual interim reports to be included in the Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) Final study report anticipated 3Q 2037

AIDS = acquired immune deficiency syndrome; GM-CSF = granulocyte macrophage colony stimulating factor; HCP = healthcare provider; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1; PBRER = Periodic Benefit Risk Evaluation Report; PEB = Physician Education Booklet; PSUR = Periodic Safety Update Report

Table 28. Other Forms of Additional Pharmacovigilance Activities

Description of Activity	Safety Concern(s)	Objectives	Milestones
For postmarketing, spontaneous reports, and reports in clinical trials, qPCR testing will also be suggested to detect talimogene laherparepvec DNA in suspected herpetic lesions	• Disseminated herpetic infection • Accidental exposure of HCP to talimogene laherparepvec • Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients • Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection	To monitor talimogene laherparepvec DNA in suspected herpetic lesions in patients treated with talimogene laherparepvec in the clinical trial and postmarketing setting.	Not applicable

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned talimogene laherparepvec category 1 or 2 studies.

Table 29. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study 20130193 A postmarketing prospective cohort study of melanoma patients treated with IMLYGIC® (talimogene laherparepvec) in clinical practice to characterize the risk of herpetic infection among patients, close contacts, and health care providers; and long-term safety in treated patients. Ongoing	Estimate the incidence rate of herpetic infection detection of talimogene laherparepvec DNA among patients for up to 5 years after the first IMLYGIC dose.	• Disseminated herpetic infection • Accidental exposure of HCP to talimogene laherparepvec • Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation); • Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients; Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection; Long-term safety data; Long-term efficacy data	Annual update Final report	Annual interim reports included in the PSUR/PBRER 3Q 2037

Footnotes are defined on last page of the table

Table 29. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities (continued)				
Study 20110261 A phase 1 multi-center, open label, dose de-escalation study to evaluate the safety and efficacy of talimogene laherparepvec in pediatric subjects with advanced non-central nervous system (CNS) tumors that are amenable to direct injection. Ongoing	To evaluate the safety and tolerability of talimogene laherparepvec as assessed by incidence of dose-limiting toxicities, in pediatric subjects with advanced non-CNS tumors that are amenable to direct injection.	Pediatric patients	Final report	2Q 2023

AIDS = acquired immune deficiency syndrome; GM-CSF = granulocyte macrophage colony stimulating factor; HCP = healthcare provider; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1; PBRER = Periodic Benefit Risk Evaluation Report; PEB = Physician Education Booklet; PSUR = Periodic Safety Update Report

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 30. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Disseminated herpetic infection	Routine risk communication: • SmPC Sections 4.4, and 4.8 • Package leaflet (PL) Section 2 Other routine risk minimization measures beyond the PI: None
Accidental exposure of HCP to talimogene laherparepvec	Routine risk communication: • SmPC Sections 4.2, 4.4, and 6.6 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Details on time after treatment to avoid direct contact protective wear, and disposal are described in Section 4.2 • Instructions on how to avoid accidental spread of talimogene laherparepvec to other areas of your body or to your close contacts are described in PL Section 2 Other routine risk minimization measures beyond the PI: None
Immune-mediated adverse reactions	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Other routine risk minimization measures beyond the PI: None
Important Potential Risks	

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Footnotes, including abbreviations, are defined on last page of this table

Table 30. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks (continued)	
Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation)	Routine risk communication: • SmPC Sections 4.4 and 6.6 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Details on time after treatment to avoid direct contact protective wear, and disposal are described in Section 6.6 • Instructions on how to avoid accidental spread of talimogene laherparepvec to other areas of your body or to your close contacts are described in PL Section 2 Other routine risk minimization measures beyond the PI: None
Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients	Routine risk communication: • SmPC Section 4.4 • PL Section 2 Other routine risk minimization measures beyond the PI: None
Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection	Routine risk communication: • SmPC Sections 4.3, 4.4, and 5.3 • PL Section 2 Other routine risk minimization measures beyond the PI: None
Combination with other therapies like chemotherapy or immunosuppressive agents	Routine risk communication: • SmPC Section 4.4 • PL Section 2 Other routine risk minimization measures beyond the PI: None

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Footnotes, including abbreviations, are defined on last page of this table

Table 30. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Missing Information	
Pregnant and lactating women	Routine risk communication: • SmPC Sections 4.4, 4.6, and 5.3 • PL Section 2 Other routine risk minimization measures beyond the PI: None
Pediatric patients	Routine risk communication: • SmPC Section 4.2 • PL Section none Other routine risk minimization measures beyond the PI: None
Long-term safety data	Routine risk communication: None Other routine risk minimization measures beyond the PI: None
Long-term efficacy data	Routine risk communication: None Other routine risk minimization measures beyond the PI: None
Treatment of patients with metastatic lesions greater than 3 cm	Routine risk communication: None Other routine risk minimization measures beyond the PI: None

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AIDS = acquired immune deficiency syndrome; GM-CSF = granulocyte macrophage colony stimulating factor; HCP = healthcare provider; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1; PI = Product Information; PL = package leaflet; SmPC = Summary of Product Characteristics

V.2 Additional Risk Minimization Measures

Table 31. Additional Risk Minimization Measure: Managed Distribution Program

Objectives	Objectives of the managed distribution program are to: • manage the product supply chain to ensure that cold storage requirements are observed (-90°C to - 70°C) • control distribution to centers which commit to: - trained healthcare providers (HCPs) to minimize the risk of specified adverse drug reactions in HCPs, patients, and close contacts of patients - train HCPs and support personnel regarding safe and appropriate storage, handling, and administration, and clinical follow-up for patients - provide specified safety information to patients and communicate to patients the importance of sharing this information with family and caregivers - trained HCPs to record batch number information in patients' charts for all injections and to provide the batch number when reporting adverse drug reactions
Rationale for the additional risk minimization activity	To manage the product supply chain to ensure that cold storage requirements are observed and to control the distribution of talimogene laherparepvec to qualified centers.
Target audience and planned distribution path	• Potential medical centers are identified based on whether they meet certain criteria/requirements for handling and administration of talimogene laherparepvec. • After it has been determined that the medical center meets the initial criteria/requirements, Amgen qualifies the medical center by conducting specific education and training of key site personnel. • The written confirmation of this specific education and training constitutes a mandatory part of the required documentation for talimogene laherparepvec customer approval via Amgen Operations Department prior to any talimogene laherparepvec delivery.

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Footnotes, including abbreviations, are defined on last page of this table.

Table 31. Additional Risk Minimization Measure: Managed Distribution Program

Plans to evaluate the effectiveness of the interventions and criteria for success	Amgen Supply Chain/Operations have a process in place to ensure that only authorized sites are supplied with talimogene laherparepvec. Effectiveness of the managed distribution program will be measured by conducting an internal evaluation of managed distribution process metrics. The main outcome measures will be the: • Proportion of centers that received talimogene laherparepvec who were trained and qualified. This will be measured by comparing listings of distributed versus qualified centers (success criteria = 100%). • Proportion of physicians who are informed about important risks associated with talimogene laherparepvec and attest to knowledge of training (% signed confirmation from signature in the Site Qualification Form; success criteria = 100%).
Evaluation of the effectiveness of risk minimization activities	Not yet assessed

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HCP = healthcare provider

Table 32. Additional Risk Minimization Measure: Physician Education Booklet

Objectives	To inform HCPs about important risks associated with talimogene laherparepvec (disseminated herpetic infection, potential harm to the fetus or neonate in pregnancy, herpetic infection in talimogene laherparepvec-treated patients, and accidental exposure of close contacts and HCPs to talimogene laherparepvec).
Rationale for the additional risk minimization activity	Educational tool to enhance HCPs' awareness about important risks associated with talimogene laherparepvec, the precautions for safe use and handling, reporting of adverse reactions and the use of talimogene laherparepvec during pregnancy.
Target audience and planned distribution path	Target audience for the Physician Education Booklet (PEB) distribution are the prescribers and other HCPs. The PEB is provided in conjunction with the specific education and training session. Resupply method as deemed appropriate is available according to local requirements.
Plans to evaluate the effectiveness of the interventions and criteria for success	Distribution of the PEB is tracked as part of the managed distribution process. Indicators of the PEB distribution include a description of the target population (ie, physicians prescribing talimogene laherparepvec), a timeline of activities, and the proportion of these physicians receiving the PEB. Effectiveness of the PEB will be measured using a cross-sectional survey to evaluate physician knowledge of safety messages included in the PEB for talimogene laherparepvec (Study 20180099). The primary endpoints will be the percentage of physicians with correct responses to the knowledge-related questions (success criteria = 80% for $n \geq 30$). The secondary endpoints will be the percentage of physicians who recall receiving and reading the talimogene laherparepvec PEB, and distributing the patient-directed materials to their patients.
Evaluation of the effectiveness of risk minimization activities	From Study 20180099, most physicians (86.7%) reported receiving the educational materials, and of those, 100% reported using the materials. For the physicians who participated in this study, physicians had generally good knowledge of the key messages included in the IMLYGIC PEB. Among the 26 questions across six knowledge domains, 21 (84%) of the questions had knowledge levels >50%, and 18 (69%) had knowledge levels ≥70%. Due to the small number (n = 15) of physicians who participated in this Study 20180099, results should be interpreted with caution. Based on the results from Study 20180099, additional steps to improve HCPs knowledge on important information by conducting refresher trainings for key physicians at qualified centers by using an online education platform focusing on the 8 subitems that scored <70% knowledge level have been proposed. Physcians are encouraged to complete the online refresher training and knowledge check within 3 months. Appropriate reminders will be sent after 2 months and additional communications will be initiated if training is not completed after 3 months (approved by EMA in September 2021 [EMEA/H/C/002771/II/0044]).

HCP = healthcare provider; PEB = Physician Education Booklet

Table 33. Additional Risk Minimization Measure: Patient Safety Brochure

Objectives	To provide important safety information for patients, including information patients can share with family, caregivers, and close contacts, and information on the risks of transmission of talimogene laherparepvec, herpetic infection, and serious infection in immunocompromised individuals.
Rationale for the additional risk minimization activity	Educational tools targeting patients to enhance their awareness of the important safety information they should know before and during talimogene laherparepvec treatment.
Target audience and planned distribution path	Patient safety brochures (PSB) are provided to prescribing physicians for distribution to patients receiving talimogene laherparepvec.
Plans to evaluate the effectiveness of the interventions and criteria for success	Distribution of the patient safety brochure and patient alert card are tracked as part of the managed distribution process.
Evaluation of the effectiveness of risk minimization activities	From Study 20180062, most (82.0%) of patients received the PSB. Of patients who received the PSB, most (93.3%) of patients read all or some of the PSB. A pre-defined success criterion of at least 60% of patients correctly answering each question within these 8 key domains was considered a threshold for knowledge of that safety message. The success criteria threshold was met by 43% of the survey questions. While patients were aware that Imlygic was an oncolytic drug that contains a weakened form of herpes simplex virus type 1, they did not meet the 60% knowledge threshold for understanding that they could develop cold sores or a more serious herpes infection, or of the signs and symptoms of a herpes infection, or of the risk to an unborn baby during pregnancy. Patients met the knowledge threshold of most of the safe hygiene practices and ways to reduce the likelihood of infecting others; but they did not meet the knowledge threshold for how long these safety actions should be taken after treatment had ended. Based on the results from Study 20180062, updates to education materials to improve the patients' knowledge on important information included in the PSB and the Patient Safety Card by additional information and design modifications to highlight important issues throughout the educational materials including the guidance for physicians have been proposed (approved by CHMP July 2022 [EMEA/H/C/002771/II/0051]). No amendment of the key messages in the RMP is needed.

CHMP = Committee for Medicinal Products for Human Use; PSB =Patient Safety Brochure

Table 34. Additional Risk Minimization Measure: Patient Alert Card

Objectives	Intended for the patient to present to HCPs upon consultation or hospitalization and informs that the holder has been treated with talimogene laherparepvec.
Rationale for the additional risk minimization activity	To ensure that specific information regarding the patient's talimogene laherparepvec therapy to refer the reader to the SmPC and Package Leaflet, and provides contact details for further information. Provides details about talimogene laherparepvec treatment start date, batch number, date administered, product manufacturer and license holder.
Target audience and planned distribution path	The target audience is the patient to present to healthcare providers upon consultation or hospitalization. Patient alert cards are provided to prescribing physicians for distribution to patients receiving talimogene laherparepvec.
Plans to evaluate the effectiveness of the interventions and criteria for success	Distribution of the patient safety brochure and patient alert card are tracked as part of the managed distribution process.
Evaluation of the effectiveness of risk minimization activities	A pre-defined success criterion of at least 60% of patients correctly answering each question within these 8 key domains was considered a threshold for knowledge of that safety message. The success criteria threshold was met by 43% of the survey questions. While patients were aware that Imlygic was an oncolytic drug that contains a weakened form of herpes simplex virus type 1, they did not meet the 60% knowledge threshold for understanding that they could develop cold sores or a more serious herpes infection, or of the signs and symptoms of a herpes infection, or of the risk to an unborn baby during pregnancy. Patients met the knowledge threshold of most of the safe hygiene practices and ways to reduce the likelihood of infecting others; but they did not meet the knowledge threshold for how long these safety actions should be taken after treatment had ended. Only 34.0% of patients received the Patient Alert Card. Based on the results from Study 20180062, updates to education materials to improve the patients' knowledge on important information included in the Patient Safety brochure and the Patient Safety Card by additional information and design modifications to highlight important issues throughout the educational materials including the guidance for physicians have been proposed (approved by CHMP July 2022 [EMEA/H/C/002771/II/0051]). No amendment of the key messages in the RMP is needed.

CHMP = Committee for Medicinal Products for Human Use; HCP = healthcare provider; SmPC = Summary of Product Characteristics

V.3 Summary of Risk Minimization Measures

Table 35. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Disseminated herpetic infection	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse event follow-up form for suspected IMLYGIC (talimogene laherparepvec) herpes virus associated adverse event • Follow-up form for clinical trial or postmarket talimogene laherparepvec associated adverse event for HCP or close contact Additional pharmacovigilance activities: • Study 20130193 • qPCR testing for talimogene laherparepvec DNA
Accidental exposure of HCP to talimogene laherparepvec	Routine risk communication: • SmPC Sections 4.2, 4.4, and 6.6 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse event follow-up form for suspected IMLYGIC (talimogene laherparepvec) herpes virus associated adverse event • Follow up form for clinical trial or postmarket talimogene laherparepvec associated adverse event for HCP or close contact Additional pharmacovigilance activities: • Study 20130193 • qPCR testing for talimogene laherparepvec DNA

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Footnotes, including abbreviations, are defined on last page of this table

Table 35. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Immune-mediated adverse reactions	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up form for suspected IMLYGIC autoimmune adverse event Additional pharmacovigilance activities: None
Important Potential Risks		
Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation)	Routine risk communication: • SmPC Sections 4.4 and 6.6 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse event follow-up form for suspected IMLYGIC (talimogene laherparepvec) herpes virus associated adverse event • Follow up form for clinical trial or postmarket talimogene laherparepvec associated adverse event for HCP or close contact Additional pharmacovigilance activities: • Study 20130193 qPCR testing for talimogene laherparepvec DNA

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Footnotes, including abbreviations, are defined on last page of this table

Table 35. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation)	Routine risk communication: • SmPC Sections 4.4 and 6.6 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse event follow-up form for suspected IMLYGIC (talimogene laherparepvec) herpes virus associated adverse event • Follow up form for clinical trial or postmarket talimogene laherparepvec associated adverse event for HCP or close contact Additional pharmacovigilance activities: • Study 20130193 • qPCR testing for talimogene laherparepvec DNA
Symptomatic talimogene laherparepvec infection in non-tumor tissue in treated patients	Routine risk communication: • SmPC Section 4.4 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse event follow-up form for suspected IMLYGIC (talimogene laherparepvec) herpes virus associated adverse event Additional pharmacovigilance activities: • Study 20130193 • qPCR testing for talimogene laherparepvec DNA

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Footnotes, including abbreviations, are defined on last page of this table

Table 35. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients	Routine risk communication: • SmPC Section 4.4 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse event follow-up form for suspected IMLYGIC (talimogene laherparepvec) herpes virus associated adverse event Additional pharmacovigilance activities: • Study 20130193 • qPCR testing for talimogene laherparepvec DNA
Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection	Routine risk communication: • SmPC Sections 4.3, 4.4, and 5.3 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Study 20130193 • qPCR testing for talimogene laherparepvec DNA
Combination with other therapies like chemotherapy or immunosuppressive agents	Routine risk communication: • SmPC Section 4.4 • PL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

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Footnotes, including abbreviations, are defined on last page of this table

Table 35. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing Information		
Pregnant and lactating women	Routine risk communication: • SmPC Sections 4.4, 4.6, and 5.3 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Pregnancy and lactation follow-up forms Additional pharmacovigilance activities: • None
Pediatric patients	Routine risk communication: • SmPC Section 4.2 • PL Section none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Study 20110261
Long-term safety data	Routine risk communication: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Study 20130193
Long-term efficacy data	Routine risk communication: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Study 20130193
Treatment of patients with metastatic lesions greater than 3 cm	Routine risk communication: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

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AIDS = acquired immune deficiency syndrome; GM-CSF = granulocyte macrophage colony stimulating factor; HCP = healthcare provider; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1; PL = package leaflet; qPCR = quantitative polymerase chain reaction; SmPC = Summary of Product Characteristics

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the RMP for talimogene laherparepvec is presented below.

Summary of Risk Management Plan for Imlygic® (Talimogene Laherparepvec)

This is a summary of the risk management plan (RMP) for Imlygic. The RMP details important risks of Imlygic, how these risks can be minimized, and how more information will be obtained about Imlygic's risks and uncertainties (missing information).

Imlygic's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Imlygic should be used.

This summary of the RMP for Imlygic should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Imlygic's RMP.

I. The medicine and what it is used for

Imlygic is authorized for treatment of adults with unresectable (cannot be removed by surgery) melanoma (a kind of skin cancer) that is regionally (in the skin or lymph nodes near the original skin tumor) or distantly metastatic (spread to distant areas of skin or lymph nodes) (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral (internal organ) disease. It contains talimogene laherparepvec as the active substance and it is given by intralesional injection (injection into the tumor).

Further information about the evaluation of Imlygic's benefits can be found in Imlygic's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: https://www.ema.europa.eu/medicines/human/EPAR/Imlygic.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Imlygic, together with measures to minimize such risks and the proposed studies for learning more about Imlygic's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (eg, with or without prescription) can help to minimizes its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Imlygic, these measures are supplemented with *additional risk minimization measures* mentioned under relevant risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Imlygic is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Imlygic are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Imlygic. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Disseminated herpetic infection • Accidental exposure of healthcare provider to talimogene laherparepvec • Immune-mediated adverse reactions
Important potential risks	• Transmission of talimogene laherparepvec from patient to close contacts or healthcare providers via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type herpes simplex virus type 1 in patients • Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection • Combination with other therapies like chemotherapy or immunosuppressive agents
Missing Information	• Pregnant and lactating women • Pediatric patients • Long-term safety data • Long-term efficacy data • Treatment of patients with metastatic lesions greater than 3 cm

II.B. Summary of Important Risks

Important Identified Risk: Disseminated herpetic infection	
Evidence for linking the risk to the medicine	This important identified risk was identified based on clinical and nonclinical data.
Risk factors and risk groups	Individuals with any congenital or acquired cellular and/or humoral immune deficiency.
Risk minimization measures	Routine risk measures: • SmPC Sections 4.4 and 4.8 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 • Quantitative polymerase chain reaction (qPCR) testing for talimogene laherparepvec DNA (a laboratory test to detect the presence of talimogene laherparepvec DNA) See Section II.C of this summary for an overview of the postauthorization development plan

Important Identified Risk: Accidental exposure of healthcare provider to talimogene laherparepvec	
Evidence for linking the risk to the medicine	This risk was identified based on reports in the clinical study setting.
Risk factors and risk groups	Numerous factors, some modifiable and some not, place healthcare providers at an increased risk for accidental exposure such as sustaining a needle stick injury. These factors include occupation, training, proper disposal of sharps, and medical activity being performed (National Institute for Occupational Safety and Health, DHHS (NIOSH), 1999; Publication No. 2000-2108).
Risk minimization measures	Routine risk communication: • SmPC Sections 4.2, 4.4, and 6.6 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 • qPCR testing for talimogene laherparepvec DNA See Section II.C of this summary for an overview of the postauthorization development plan

Important Identified Risk: Immune-mediated adverse reactions	
Evidence for linking the risk to the medicine	This is considered an important identified risk based on reports in the clinical study setting.
Risk factors and risk groups	Risk factors for an immune-mediated adverse reaction include host factors (eg, demographics, other comorbidities), host genotypes (Thong and Tan, *Br J Clin Pharmacol,* 2011; 71:684-700), and pre-existing autoimmune disease.
Risk minimization measures	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Additional risk minimization measures: None

Important Potential Risk: Transmission of talimogene laherparepvec from patient to close contacts or healthcare providers via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation)	
Evidence for linking the risk to the medicine	This risk is considered an important potential risk based on clinical and nonclinical data.
Risk factors and risk groups	Direct contact with injected lesions, protective dressings, or body fluids of treated patients. The likelihood of transfer of talimogene laherparepvec to a close contact or healthcare provider increases if the contact has a break in the skin or mucous membranes.
Risk minimization measures	Routine risk communication: • SmPC Sections 4.4 and 6.6 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 • qPCR testing for talimogene laherparepvec DNA See Section II.C of this summary for an overview of the postauthorization development plan

Important Potential Risk: Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type herpes simplex virus type 1 in patients	
Evidence for linking the risk to the medicine	This risk is considered an important potential risk based on nonclinical data.
Risk factors and risk groups	Previous infection with wild-type herpes simplex virus type 1. Fever, stress, and other factors are common triggers of recurrence.
Risk minimization measures	Routine risk communication: • SmPC Section 4.4 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities:

	• Study 20130193 • qPCR testing for talimogene laherparepvec DNA See Section II.C of this summary for an overview of the postauthorization development plan
Important Potential Risk: Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection	
Evidence for linking the risk to the medicine	This important potential risk was identified based on theoretical concern and limited data with immunocompromised patients treated with talimogene laherparepvec.
Risk factors and risk groups	Immunosuppression can be due to congenital immunodeficiency, acquired disease (HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, generalized malignancy), pharmacotherapy (immunosuppressive agents, radiation or large amounts of corticosteroids), or extremes of age (neonates and elderly) (Chinen and Shearer, *J Allergy Clin Immunol*, 2010; 125(suppl 2):195-203; Notarangelo, *J Allergy Clin Immunol*, 2010; 125(suppl 2):182-194). The precise risk factors applicable to this risk with talimogene laherparepvec are unknown.
Risk minimization measures	Routine risk communication: • SmPC Sections 4.3, 4.4, and 5.3 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 • qPCR testing for talimogene laherparepvec DNA See Section II.C of this summary for an overview of the postauthorization development plan

Important Potential Risk: Combination with other therapies like chemotherapy or immunosuppressive agents	
Evidence for linking the risk to the medicine	This is considered an important potential risk based on nonclinical data from immunocompromised mice.
Risk factors and risk groups	Patients receiving concomitant chemotherapeutic or immunosuppressive therapies.
Risk minimization measures	Routine risk communication: • SmPC Section 4.4 • PL Section 2

Missing Information: Pregnant and lactating women	
Risk minimization measures	Routine risk communication: • SmPC Sections 4.4, 4.6, and 5.3 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20180062 See Section II.C of this summary for an overview of the postauthorization development plan

Missing Information: Pediatric patients	
Risk minimization measures	Routine risk communication: • SmPC Section 4.2 • PL Section none Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20110261 See Section II.C of this summary for an overview of the postauthorization development plan

Missing Information: Long-term safety data	
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 See Section II.C of this summary for an overview of the postauthorization development plan

Missing Information: Long-term efficacy data	
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 See Section II.C of this summary for an overview of the postauthorization development plan

Missing Information: Treatment of patients with metastatic lesions greater than 3 cm	
Risk minimization measures	No risk minimization measures

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

Not applicable.

II.C.2. Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
Study 20130193 A postmarketing prospective cohort study of melanoma patients treated with IMLYGIC® (talimogene laherparepvec) in clinical practice to characterize the risk of herpetic infection among patients, close contacts, and health care providers; and long-term safety in treated patients.	Estimate the incidence rate of herpetic infection detection of talimogene laherparepvec DNA among patients for up to 5 years after the first IMLYGIC dose. Safety concerns addressed: • Disseminated herpetic infection • Accidental exposure of healthcare provider to talimogene laherparepvec • Transmission of talimogene laherparepvec from patient to close contacts or healthcare providers via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type herpes simplex virus type 1 in patients • Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection • Long-term safety data • Long-term efficacy data
Study 20110261 A phase 1 multi-center, open label, dose de-escalation study to evaluate the safety and efficacy of talimogene laherparepvec in pediatric subjects with advanced non-central nervous system (outside brain and spinal cord) tumors that are amenable to direct injection.	To evaluate the safety and tolerability of talimogene laherparepvec as assessed by incidence of dose-limiting toxicities, in pediatric subjects with advanced non-central nervous system tumors that are amenable to direct injection. Safety concerns addressed: Pediatric patients

PART VII: ANNEXES

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Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Table of Contents

AMGEN

Report of Suspected IMLYGIC® (Talimogene laherparepvec) or Herpes Virus Associated Adverse Event

AER#

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Do not provide information by or through which a patient can be identified, other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as dd/mm/yyyy)

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

Gender: ☐ Male ☐ Female

Age at time of event: _____

Event Reported Term

Relationship: ☐ Patient ☐ Close contact ☐ Health Care Professional ☐ Other

Study Number (if applicable)

☐ Clinical Trial ☐ Observational study ☐ Post-marketing

IMLYGIC (TVEC) ADMINISTRATION, if applicable (Please indicate dates as dd/mm/yyyy)

IMLYGIC Dose _____ Frequency _____ Route _____

IMLYGIC Batch # _____ Exp Date _____ ☐ Batch # unknown

IMLYGIC first dose (date) _____ IMLYGIC last dose (date) _____

Were any doses of IMLYGIC skipped? ☐ Yes ☐ No ☐ Unknown _____

If yes, please specify dates and reason _____

IMLYGIC discontinued ☐ Yes ☐ No ☐ Unknown _____

If yes, date of last dose/discontinuation _____

SIGNS AND SYMPTOMS (Check all that apply, provide dates of onset, resolution if available)

☐ Previous history of herpes infections:

Last episode (dd/mm/yyyy) _____

☐ Location of Lesion (Please describe) _____

☐ Since the time of exposure or suspected exposure to IMLYGIC, indicate sign/symptoms of herpes infection (Specify area: skin, oral, genital, eyes, etc.)

☐ No signs/symptoms post-accidental exposure

Describe how exposure occurred:

☐ Physical contact
☐ Touched lesion
☐ Close contact
☐ Sleep together
☐ Caregiver
☐ Dressing change
☐ Others _____

IMLYGIC PCR swab done? ☐ Yes ☐ No

If yes, provide date(s) lesion(s) were swabbed:

Provide anatomical location(s) of lesion(s) swabbed:

If no, indicate reason swab was not done:

Swabbed for herpes simplex virus type-1 (HSV-1) and/or has the diagnosis been confirmed with any laboratory tests? (If yes, please provide results in table below)

☐ Yes ☐ No ☐ Don't know

Treated with antivirals (eg, acyclovir) for a herpes infection?

☐ Yes (date) _____ ☐ No ☐ Don't know

Details: _____

Method of treatment administration:

☐ Topical ☐ Oral ☐ Intravenous

Pregnant: ☐ Yes ☐ No

Details: _____

EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (Please indicate and attach copy of report if available)

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached Y	Report Attached N
Results at BASELINE for HSV (prior to IMLYGIC)					
PCR					
Other (specify)					

Diagnostic	Tests for: HSV	Tests for: IMLYGIC	Results/Units	Reference Range/Units	Date	Report Attached Y	Report Attached N
Results at TIME OF EVENT							
PCR							
Other (specify)							

Return completed form to Amgen via email: svc-ags-in-us@amgen.com or fax: 1-888-814-8653

Reporter Name

CONTINUED ON NEXT PAGE

AMGEN

Report of Suspected IMLYGIC® (Talimogene laherparepvec) or Herpes Virus Associated Adverse Event (continued)

AER #

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CONCOMITANT MEDICATIONS (Please indicate and provide dates dd/mm/yyyy)

Concomitant Medications: ☐ Yes ☐ No (Please provide dose, start and stop dates):

Immunosuppressive Medications: ☐ Yes ☐ No (Please provide dose, start and stop dates):

Co-suspect Medications: ☐ Yes ☐ No

REPORTS/RELEVANT FINDINGS (Please provide dates, baseline information and indicate attachments if available)

☐ X-ray

☐ MRI

☐ CT

☐ Hospital discharge report

☐ Other consult report

☐ Provide final diagnosis and treatment, if available (please specify)

☐ Outcome and resolution date

PATIENT HISTORY/RISK FACTORS (Please provide history, dates, severity of reaction and intervention)

Please check if patient has any chronic disease or infection, etc.

☐ Immunosupression

☐ Cancer (specify)

☐ Chronic lung disease

☐ Hepatitis

☐ Chronic kidney disease

☐ Liver disease

☐ HIV

☐ Diabetes mellitus

☐ Recent wounds/infections

Please specify: (cause, description)

☐ Steroid exposure (specify)

☐ Drug or IV drug abuse (specify): Type

Amount Frequency

☐ Indwelling catheters (specify)

☐ Recent skin injury (specify)

☐ Other history/risk factors (specify)

REPORTER Name:

Address:

City:

State/ Province:

Country:

Postal Code:

Email:

Phone: (include country code)

Signature

Title Date

Return completed form to Amgen via email: svc-ags-in-us@amgen.com or fax: 1-888-814-8653.

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AMGEN

Report of Suspected IMLYGIC® (Talimogene laherparepvec) or Herpes Virus Associated Adverse Event

AER#

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PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as dd/mm/yyyy)

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

Gender: ☐ Male ☐ Female

Age at time of event: _____

Event Reported Term

Relationship: ☐ Patient ☐ Close contact ☐ Health Care Professional ☐ Other

Study Number (if applicable)

☐ Clinical Trial ☐ Observational study ☐ Post-marketing

IMLYGIC (TVEC) ADMINISTRATION, if applicable (Please indicate dates as dd/mm/yyyy)

IMLYGIC Dose _____ Frequency _____ Route _____

IMLYGIC Batch # _____ Exp Date _____ ☐ Batch # unknown

IMLYGIC first dose (date) _____ IMLYGIC last dose (date) _____

Were any doses of IMLYGIC skipped? ☐ Yes ☐ No ☐ Unknown _____

If yes, please specify dates and reason _____

IMLYGIC discontinued ☐ Yes ☐ No ☐ Unknown _____

If yes, date of last dose/discontinuation _____

SIGNS AND SYMPTOMS (Check all that apply, provide dates of onset, resolution if available)

☐ Previous history of herpes infections:

Last episode (dd/mm/yyyy) _____

☐ Location of Lesion (Please describe) _____

☐ Since the time of exposure or suspected exposure to IMLYGIC, indicate sign/symptoms of herpes infection (Specify area: skin, oral, genital, eyes, etc.)

☐ No signs/symptoms post-accidental exposure

Describe how exposure occurred:

☐ Physical contact
☐ Touched lesion
☐ Close contact
☐ Sleep together
☐ Caregiver
☐ Dressing change
☐ Others _____

IMLYGIC PCR swab done? ☐ Yes ☐ No

If yes, provide date(s) lesion(s) were swabbed:

Provide anatomical location(s) of lesion(s) swabbed:

If no, indicate reason swab was not done:

Swabbed for herpes simplex virus type-1 (HSV-1) and/or has the diagnosis been confirmed with any laboratory tests? (If yes, please provide results in table below)

☐ Yes ☐ No ☐ Don't know

Treated with antivirals (eg, acyclovir) for a herpes infection?

☐ Yes (date) _____ ☐ No ☐ Don't know

Details: _____

Method of treatment administration:

☐ Topical ☐ Oral ☐ Intravenous

Pregnant: ☐ Yes ☐ No

Details: _____

EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (Please indicate and attach copy of report if available)

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached Y	Report Attached N
Results at BASELINE for HSV (prior to IMLYGIC)					
PCR					
Other (specify)					

Diagnostic	Tests for: HSV	Tests for: IMLYGIC	Results/Units	Reference Range/Units	Date	Report Attached Y	Report Attached N
Results at TIME OF EVENT							
PCR							
Other (specify)							

Return completed form to Amgen via email or fax.

Reporter Name

CONTINUED ON NEXT PAGE

AMGEN

Report of Suspected IMLYGIC® (Talimogene laherparepvec) or Herpes Virus Associated Adverse Event (continued)

AER #

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CONCOMITANT MEDICATIONS (Please indicate and provide dates dd/mm/yyyy)

Concomitant Medications: ☐ Yes ☐ No (Please provide dose, start and stop dates):

Immunosuppressive Medications: ☐ Yes ☐ No (Please provide dose, start and stop dates):

Co-suspect Medications: ☐ Yes ☐ No

REPORTS/RELEVANT FINDINGS (Please provide dates, baseline information and indicate attachments if available)

☐ X-ray

☐ MRI

☐ CT

☐ Hospital discharge report

☐ Other consult report

☐ Provide final diagnosis and treatment, if available (please specify)

☐ Outcome and resolution date

PATIENT HISTORY/RISK FACTORS (Please provide history, dates, severity of reaction and intervention)

Please check if patient has any chronic disease or infection, etc.

☐ Immunosupression

☐ Cancer (specify)

☐ Chronic lung disease

☐ Hepatitis

☐ Chronic kidney disease

☐ Liver disease

☐ HIV

☐ Diabetes mellitus

☐ Recent wounds/infections

Please specify: (cause, description)

☐ Steroid exposure (specify)

☐ Drug or IV drug abuse (specify): Type

Amount Frequency

☐ Indwelling catheters (specify)

☐ Recent skin injury (specify)

☐ Other history/risk factors (specify)

REPORTER Name:

Address:

City:

State/ Province:

Country:

Postal Code:

Email:

Phone: (include country code)

Signature

Title Date

Return completed form to Amgen via email or fax.

CONTINUED FROM PREVIOUS PAGE

A Study # xxxxxxxx	**Clinical Trial Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact** ***Notify Amgen Within 24 hours of awareness***	❑**New** ❑**Follow-up**

SELECT OR TYPE IN A FAX#

SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

INFORMATION FOR THE PERSON EXPERIENCING EVENT

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

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

☐ Health care professional	☐ Close contact who is: ☐ Residing with treated subject ☐ Providing medical assistance/care to subject ☐ Regularly in close contact with treated subject

1. Talimogene laherparepvec administration to the treated subject (if known)

a. Date of first dose administration

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

b. Date of last dose administration

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

☐ Not applicable (e.g. exposure occurred during administration preparation)

Product Lot Number: _____ or Unknown (✔):_____

2. History of person experiencing event

a. Previous history of herpes infections

☐ No

☐ Yes: Date of last episode __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

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

Signs / Symptoms of herpes infections prior to known or suspected exposure to TVEC	Present	How many times per year?
Cold sores/fever blisters: ☐ Oral ☐ Genital		
Other suspected symptoms (describe): _____		

c. Has the person ever been treated with antivirals, eg, acyclovir, for herpes infection?

☐ No ☐ Not sure ☐ Yes (Date): __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

Method of treatment administration: ☐ Topical ☐ Oral ☐ Intravenous

d. Was the person taking any medications (other than antivirals addressed in 2c above) at the time of the event?

☐ No ☐ Not sure ☐ Yes (Provide details below)

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

A Study # xxxxxxxx	**Clinical Trial Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact** ***Notify Amgen Within 24 hours of awareness***	❑New ❑Follow-up

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

Exposure Information	Check all boxes that apply to known exposure(s)	
	Physical direct contact with treated patient	**Caregiver**
Date and Exposure ID _____/_____/__________ dd mm yyyy Exposure ID: | | | - | | | ☐ Date and Exposure ID not known	☐ Sleep together ☐ Intimate physical contact (kissing, sexual intercourse) ☐ Other (describe below):	☐ Dressing change ☐ Injection site ☐ Needle stick ☐ Splash back ☐ Other (describe below):
Date and Exposure ID _____/_____/__________ dd mm yyyy Exposure ID: | | | - | | | ☐ Date and Exposure ID not known	☐ Sleep together ☐ Intimate physical contact (kissing, sexual intercourse) ☐ Other (describe below):	☐ Dressing change ☐ Injection site ☐ Needle stick ☐ Splash back ☐ Other (describe below):
Date and Exposure ID _____/_____/__________ dd mm yyyy Exposure ID: | | | - | | | ☐ Date and Exposure ID not known	☐ Sleep together ☐ Intimate physical contact (kissing, sexual intercourse) ☐ Other (describe below):	☐ Dressing change ☐ Injection site ☐ Needle stick ☐ Splash back ☐ Other (describe below):

4. Evaluations, Diagnosis & Laboratory Measures

Diagnostic	Results/Units	Reference Range/Units	Date (dd/mm/yyyy)	
Live virus assay			____/____/________	
Quantitative Polymerase Chain Reaction (PCR)			____/____/________	
Serologic test (antibody test)			____/____/________	
Other (specify):			____/____/________	
Other (specify):			____/____/________	

A Study # xxxxxxxx	**Clinical Trial Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact** ***Notify Amgen Within 24 hours of awareness***	❑**New** ❑**Follow-up**

A Study # XXXXXXXX	**Clinical Trial Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact** ***Notify Amgen Within 24 hours of awareness***	❑**New** ❑**Follow-up**

5. Adverse Event Information:

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

Signs or Symptoms	**Present?**	**Location on body**	**If Serious, enter Serious Criteria code** *(see codes below)*	**Relationship to TVEC**	**Date started** (dd/mm/yyyy)	**Date ended** (dd/mm/yyyy)
Cold sores/fever blister, eg, on face, mouth, lip or nose single or multiple red papular or ulcerated lesions at muco-cutaneous junction, around mouth or on face, with pain, tingling or itching	☐ Yes ☐ No			☐ Yes ☐ No ☐ Unknown	___/___/_____	___/___/_____
Herpetic whitlow (painful, itchy blister lesion on fingertips of hand)	☐ Yes ☐ No			☐ Yes ☐ No ☐ Unknown	___/___/_____	___/___/_____
Cold sore/ fever blister in genital area	☐ Yes ☐ No			☐ Yes ☐ No ☐ Unknown	___/___/_____	___/___/_____
Herpes keratitis - eye signs and/or symptoms (redness, pain, photophobia (intolerance to light), blurred vision, tearing)	☐ Yes ☐ No			☐ Yes ☐ No ☐ Unknown	___/___/_____	___/___/_____
Herpes simplex encephalitis - neurological signs and/or symptoms (eg, fever associated with headache, vomiting, lethargy, psychiatric symptoms, seizures, weakness, confusion, or memory loss)	☐ Yes ☐ No			☐ Yes ☐ No ☐ Unknown	___/___/_____	___/___/_____
Other signs/symptoms: (DESCRIBE)	☐ Yes ☐ No			☐ Yes ☐ No ☐ Unknown	___/___/_____	___/___/_____
Serious Criteria:	01 Fatal 02 Immediately life-threatening 03 Required hospitalization 04 Prolonged hospitalization 05 Persistent or significant disability /incapacity 06 Congenital anomaly / birth defect 07 Other significant medical hazard					

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

A Study # xxxxxxxx	**Clinical Trial Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact** ***Notify Amgen Within 24 hours of awareness***	❑**New** ❑**Follow-up**

6. Action Taken:

a. Did either of the following occur since the associated subject began treatment with Talimogene Laherparepvec?

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

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

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

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

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

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

Method of treatment administration: ☐ Topical ☐ Oral ☐ Intravenous

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

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

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

Signature of Investigator or Designee	Title	Date of report

A Study # XXXXXXXX	**Postmarket Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact** ***Notify Amgen Within one business day of awareness***	❑**New** ❑**Follow-up**

SELECT OR TYPE IN A FAX#

SITE INFORMATION (if associated patient is in a post market study)

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

INFORMATION FOR THE PERSON EXPERIENCING EVENT

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

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

☐ Health care professional	☐ Close contact who is: ☐ Residing with treated subject ☐ Providing medical assistance/care to subject ☐ Regularly in close contact with treated subject ☐ Other (specify) _____

1. Talimogene laherparepvec administration to the treated subject (if known)

a. Date of first dose administration

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

b. Date of last dose administration

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

☐ Not applicable (e.g. exposure occurred during administration preparation)

Product Lot Number: _____ or Unknown (✔):_____

A Study # xxxxxxxx	**Postmarket Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact** ***Notify Amgen Within one business day of awareness***	❑**New** ❑**Follow-up**

2. History of person experiencing event

a. Previous history of herpes infections

☐ No

☐ Yes: Date of last episode __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

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

Signs / Symptoms of herpes infections prior to known or suspected exposure to TVEC	**Present**	**How many times per year?**
Cold sores/fever blisters: ☐ Oral ☐ Genital		
Other suspected symptoms (describe): _____		

c. Has the person ever been treated with antivirals, eg, acyclovir, for herpes infection?

☐ No ☐ Not sure ☐ Yes (Date): __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

Method of treatment administration: ☐ Topical ☐ Oral ☐ Intravenous

d. Was the person taking any medications (other than antivirals addressed in 2c above) at the time of the event?

☐ No ☐ Not sure ☐ Yes (Provide details below)

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

A Study # xxxxxxxx	**Postmarket Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact** ***Notify Amgen Within one business day of awareness***	❑New ❑Follow-up

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

Exposure Information	**Check all boxes that apply to known exposure(s)**	
	Physical direct contact with treated patient	**Direct contact with Talimogene laherparepvec** (e.g. Caregiver or distributor)
Date and Exposure ID ____/____/________ dd mm yyyy Exposure ID: _ _ _ - _ _ _ ☐ Date and Exposure ID not known	☐ Sleep together ☐ Intimate physical contact (kissing, sexual intercourse) ☐ Other (describe below):	☐ Dressing change ☐ Injection site ☐ Needle stick ☐ Splash back ☐ Other (describe below):
Date and Exposure ID ____/____/________ dd mm yyyy Exposure ID: _ _ _ - _ _ _ ☐ Date and Exposure ID not known	☐ Sleep together ☐ Intimate physical contact (kissing, sexual intercourse) ☐ Other (describe below):	☐ Dressing change ☐ Injection site ☐ Needle stick ☐ Splash back ☐ Other (describe below):
Date and Exposure ID ____/____/________ dd mm yyyy Exposure ID: _ _ _ - _ _ _ ☐ Date and Exposure ID not known	☐ Sleep together ☐ Intimate physical contact (kissing, sexual intercourse) ☐ Other (describe below):	☐ Dressing change ☐ Injection site ☐ Needle stick ☐ Splash back ☐ Other (describe below):

4. Evaluations, Diagnosis & Laboratory Measures

Diagnostic	**Results/Units**	**Reference Range/Units**	**Date (dd/mm/yyyy)**	
Live virus assay			___/___/______	
Quantitative Polymerase Chain Reaction (PCR)			___/___/______	
Serologic test (antibody test)			___/___/______	
Other (specify):			___/___/______	
Other (specify):			___/___/______	

A Study # xxxxxxxx	**Postmarket Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact** ***Notify Amgen Within one business day of awareness***	❑**New** ❑**Follow-up**

A Study # XXXXXXXX	**Postmarket Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact** ***Notify Amgen Within one business day of awareness***	❑**New** ❑**Follow-up**

5. Adverse Event Information:

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

Signs or Symptoms	**Present?**	**Location on body**	**If Serious, enter Serious Criteria code** *(see codes below)*	**Relationship to TVEC**	**Date started** (dd/mm/yyyy)	**Date ended** (dd/mm/yyyy)
Cold sores/fever blister, eg, on face, mouth, lip or nose single or multiple red papular or ulcerated lesions at muco-cutaneous junction, around mouth or on face, with pain, tingling or itching	☐ Yes ☐ No			☐ Yes ☐ No ☐ Unknown	___/___/_____	___/___/_____
Herpetic whitlow (painful, itchy blister lesion on fingertips of hand)	☐ Yes ☐ No			☐ Yes ☐ No ☐ Unknown	___/___/_____	___/___/_____
Cold sore/ fever blister in genital area	☐ Yes ☐ No			☐ Yes ☐ No ☐ Unknown	___/___/_____	___/___/_____
Herpes keratitis - eye signs and/or symptoms (redness, pain, photophobia (intolerance to light), blurred vision, tearing)	☐ Yes ☐ No			☐ Yes ☐ No ☐ Unknown	___/___/_____	___/___/_____
Herpes simplex encephalitis - neurological signs and/or symptoms (eg, fever associated with headache, vomiting, lethargy, psychiatric symptoms, seizures, weakness, confusion, or memory loss)	☐ Yes ☐ No			☐ Yes ☐ No ☐ Unknown	___/___/_____	___/___/_____
Other signs/symptoms: (DESCRIBE)	☐ Yes ☐ No			☐ Yes ☐ No ☐ Unknown	___/___/_____	___/___/_____
Serious Criteria:	01 Fatal 02 Immediately life-threatening 03 Required hospitalization 04 Prolonged hospitalization 05 Persistent or significant disability /incapacity 06 Congenital anomaly / birth defect 07 Other significant medical hazard					

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

A Study # xxxxxxxx	**Postmarket Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact** ***Notify Amgen Within one business day of awareness***	❑**New** ❑**Follow-up**

6. Action Taken:

a. Did either of the following occur since the associated subject began treatment with Talimogene Laherparepvec?

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

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

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

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

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

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

Method of treatment administration: ☐ Topical ☐ Oral ☐ Intravenous

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

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

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

Signature of Investigator or Designee	Title	Date of report

AMGEN®

Report of Suspected IMLYGIC™ (Talimogene laherparepvec) Autoimmune Adverse Event

AER #

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PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier Number

Patient Initials

Date of Event Onset

Date of This Report

Gender: ☐ Male ☐ Female

Event Reported Term

Study Number (if applicable)

Age at Time of Event or Date of Birth:_____ Ethnicity:_____

☐ Clinical Trial ☐ Observational Study ☐ Post Marketing

IMLYGIC™ ADMINISTRATION (Please indicate dates as DD/MM/YYYY)

IMLYGIC™ Dose _____ Concentration: ☐ 10^6 PFU/mL ☐ 10^8 PFU/mL

Lesions/Locations Injected: _____

Frequency _____ Route _____

IMLYGIC™ Batch #_____ Exp Date _____ ☐ Batch # unknown

SIGNS AND SYMPTOMS (Check all that apply, provide dates of onset, resolution if available)

☐Fever/Body Temperature: _____
Recurrent fever, high body temperature (>101°F or 38.3°C)

☐Hair: (specify) _____

☐Skin: (specify) _____

☐Hemodynamic: (specify)_____

☐Eyes: (specify) _____

☐Hands and Feet: (specify) _____

☐Throat, Neck, Voice, and Mouth: (specify)

☐Fatigue and Sleep: (specify) _____

☐Lungs: (specify) _____

☐Heart: ((specify) _____

☐Endocrine: (specify) _____

☐Metabolism: (specify) _____

☐Muscles, Joints, and Tendons:(specify)

☐Digestion/Gastrointestinal: (specify) _____

☐Renal: (specify) _____

☐Mood and Thinking: (specify) _____

☐Balance, Coordination, and Neurological symptoms:
(specify)_____

Other _____

MEDICAL HISTORY / RiSK FACTORS (Check all that apply)

☐History of autoimmune diseases: (specify)

☐History of chronic pancreatitis: (specify)

☐History of malignancy (other than melanoma): (specify)

☐History of infections: (specify)

☐History of medication allergy: (specify)

☐Immunosuppressive agents (eg, TNF-inhibitors): (specify)

☐Other relevant concomitant medication(s):

☐Prior therapies for melanoma (eg, Ipilimumab, Pembrolizumab) with dates of therapy, reason for discontinuation: (specify)

☐History of blood transfusion: (specify)

☐Other relevant medical history: (specify)

Additional Information: _____

Return completed form to Amgen via email: svc-ags-in-us@amgen.com or fax: 1-888-814-8653

Reporter
Name

CONTINUED ON NEXT PAGE

AMGEN®

Report of Suspected IMLYGIC™ (Talimogene laherparepvec) Autoimmune Adverse Event (continued)

AER #

EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (Please indicate and attach copy of report if available)

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached Y	Report Attached N
CBC					
Hgb					
Hct					
RBC/reticulocyte count					
Platelet count					
Others (specify)					
WBC					
Neutrophils					
Lymphocytes					
Others (specify)					
Others (specify)					
Cortisol					
LH					
ACTH					
FSH					
Monoclonal/polyclonal					
Serum chemistry					
Fasting glucose					
Random glucose					
HbA1c					
Others (specify)					

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached Y	Report Attached N
Electrolyte					
ALT					
AST					
Direct/total bilirubin					
Alkaline phosphatase					
BUN					
Serum creatinine					
ANA					
C-reactive protein					
CPK					
ds DNA titer					
Antiphospholipid antibodies					
Anti-Smith antibodies					
Combs test (indirect, direct)					
TSH					
T3					
T4					
Immunoglobulin					
Antimitochondrial antibody					
Acetylcholine receptor antibodies					
Others (specify)					

REPORTS / RELEVANT FINDINGS (Check all that apply, attach copy of report if available)

☐ CT scan _____

☐ Ultrasonography _____

☐ MRI _____

☐ PET with 18F-fluorodeoxyglucose _____

☐ Retrograde/percutaneous antegrade pyelography _____

☐ Chest X-ray _____

☐ Biopsy of mass _____

☐ Electrocardiogram _____

☐ Was there a final diagnosis or etiology? _____

☐ Hospital admission/discharge report _____

☐ Other consult report _____

_____

_____

Return completed form to Amgen via email: svc-ags-in-us@amgen.com or fax: 1-888-814-8653

REPORTER Name: _____

Address: Email: State/Province:

City: Phone: Postal Code:

Country

Signature _____ Title _____ Date _____

CONTINUED FROM PREVIOUS PAGE

INITIAL PREGNANCY (MOTHER) AUTHORIZATION AND QUESTIONNAIRE

From: {Title} {First Name} {Last Name} {Company Name} {Country}	[today]
To: [reporter_first_name]:[1] [reporter_last_name]:[1]	

Event: Pregnancy	**Product**: [product_name]:[1]
AER#: [case_id]	**Reply Due By**: {Due Date}

Dear [reporter_first_name]:[1] [reporter_last_name]:[1],

Thank you for reporting your [patient_initials] pregnancy while on [product_name:first_suspect] ([generic_name:first_suspect]) therapy. Please send the completed questionnaire and signed consent form with requested information to the address, email or fax below.

Kindly note the following attachments:

- **AUTHORIZATION FOR RELEASE OF PREGNANCY AND INFANT HEALTH INFORMATION**
- **INITIAL PREGNANCY QUESTIONNAIRE (MOTHER)**

Respectfully Yours,

{Title} {First Name} {Last Name}
{Company Name} {Country}
Email: {email}
Fax: {fax}
Phone: {phone}

Authorization for Release of Pregnancy and Infant Health Information

[This is an example of text that can be used to obtain authorization for release of information from a female who initiated an Amgen product during her pregnancy or became pregnant during treatment or after discontinuing treatment with an Amgen investigational or marketed product. It is also applicable to a pregnant woman whose male partner was taking an Amgen product when she became pregnant or initiated an Amgen product during the pregnancy]
Make alterations as directed within each square bracket [ ] that are appropriate to the region/country. This text should be altered only if required by local laws and regulations and following legal review. Discard all directions in the final form, including this one, before sending externally.]

Female Authorization Form to Obtain Pregnancy and Infant Health Information
[Authorization author: select the appropriate statement from the two options below depending on whether the female is the exposed parent or her male partner.]

[Authorization author: specify appropriate Amgen entity, e.g., Amgen Inc., Amgen Ltd., Amgen Canada] has been informed that you have become pregnant (or were already pregnant) during or after discontinuing treatment with *[add Amgen investigational or marketed product name]*.

OR

[Authorization author: specify appropriate Amgen entity, e.g., Amgen Inc., Amgen Ltd., Amgen Canada] has been informed that you have become pregnant (or were already pregnant) while your male partner was taking *[add Amgen investigational or marketed product name]*.

[Authorization author: include this information in all authorizations]
Amgen Inc. and its respective global subsidiaries and affiliates (collectively referred to as "Amgen") collects pregnancy-related health information when a woman becomes pregnant (or was already pregnant), while she, or her male partner, was taking an Amgen investigational or marketed drug product. The information collected will contribute to the body of knowledge that could ultimately help patients and their healthcare providers (HCP) make more informed decisions about taking an Amgen medication during pregnancy.

We would like to collect this information whether or not you and your partner decide, in consultation with your HCP and/or study doctor (if the pregnancy occurred during a study), to continue with this pregnancy. Although Amgen collects information about the pregnancy and birth outcome, Amgen will not be responsible for any expenses relating to this pregnancy or its outcome. We do not provide any payment or compensation to you for providing information and there are no medications or treatments prescribed.

Because we are collecting personal health information, you are required to <<sign an authorization>> *[for regions where signed authorization is required or]* <<provide authorization>> *[for regions where verbal authorization may be acceptable such as the U.S.]* for release of information concerning your pregnancy, and if applicable, the birth and health of your child(ren) born from this pregnancy. The medical information requested may include:

- your current health, your pregnancy and previous pregnancies and birth outcomes.
- your child(ren)s health information from this pregnancy (e.g., any newborn complications) up to 12 months following birth, if applicable.

[Authorization Author: Use this language if follow-up will only be conducted with the HCP]
If you agree to be a part of this pregnancy follow-up activity, Amgen will contact your HCP, and/or a study doctor (if the pregnancy occurred during a study), to request your and your child(ren)s health information. If applicable, additional information will be requested approximately 6 to 8 weeks after the estimated delivery date and when the child(ren) is/are 6 and 12 months of age. Your HCP may also contact other HCPs responsible for your or your child(ren)s medical care to obtain additional information about your health, your pregnancy, and the health of your child(ren).

OR

[Authorization Author: Use this language if (acceptable per local laws and customs) follow-up may be conducted with the HCP and/or the patient (such as the US)]

If you agree to be a part of this pregnancy follow-up activity, Amgen will contact you and/or your HCP, or the study doctor (if the pregnancy occurred during a study), to request your and your child(ren)s health information. If applicable, additional information will be requested approximately 6 to 8 weeks after the estimated delivery date and when the baby is 6 and 12 months of age. Amgen may also contact other HCPs responsible for your or your childs medical care to obtain additional information about your health, your pregnancy, and the health of your child(ren). Contact information (name, phone number, etc.) about you and your child(ren) is not collected unless you have contacted Amgen or given authorization for Amgen to contact you directly. In that case, Amgen will continue to store your contact information. However, your personal identifiable information will not be released to any outside agencies unless required by law.

[Authorization Author: Include this language for all patients/subjects]

Because Amgen medications may be taken by patients throughout the world, Amgen and its service providers have offices in many global locations. Other countries may not provide the same level of protection for your and your child(ren)s personal information as is available in *[patients home country name]*. Regardless of the country in which data is collected and processed, Amgen maintains administrative, technical and physical safeguards to protect information about you and your child(ren).

Regulatory agencies and Amgen business partners who distribute *[add Amgen investigational or marketed product name]* both within and outside *[patients home country name]* *[Authorization Author: Only include the Institutional Review Board and Ethics Committee information if the subject or father of the baby was enrolled in a study]* and the *[specify appropriate name for the party responsible for ethics review and approval e.g., Institutional Review Board (IRB), Ethics*

Committee] may review pregnancy and infant health information that Amgen collects. If you have provided your and/or your child(ren)s name and any other identifying data, this information will not be revealed, unless required by applicable law or regulation.

The information collected may also be used in future scientific research into *[specify therapeutic area]* and any related scientific or educational publications. Neither you nor your child will be identified in any such publications.

Your authorization to provide this information is completely voluntary and gives Amgen and its trusted service providers permission to obtain, store, and analyse information about you and your child(ren). You are free to withdraw authorization at any time. *[The following sentence may be used, depending on applicable laws and regulations for your country/region]:* You may also access information held about you and your child(ren), and you have the right to correct inaccuracies in the information held about you and your child(ren). If you withdraw your authorization, all information capable of identifying you or your child(ren) will be deleted from the Amgen database. Amgen may continue to use such anonymized information collected prior to the date of withdrawal. *[The following may be used, depending on applicable laws and regulations for your country/region]* In such circumstances, since the data can no longer be linked to you, we will be unable to respond to access requests.

If you have any questions at any time, or you wish to withdraw your authorization, or you wish to exercise any rights you have with respect to information collected by Amgen, including on behalf of your child(ren), please notify your doctor or write to Amgen (contact details given below).

Thank you for your willingness to provide Amgen this with important information.

By signing this authorization form, I confirm that I understand the terms above and agree to allow the collection of my and my child(ren)s personal health information.

Mother Full Name *(Printed)*	Signature	Date

Authorization on Behalf of Child

By signing this authorization form, I confirm that I agree that my child(ren) (born from this pregnancy) will take part in this activity and is/are subject to the same terms described above.

Child Full Name (as applicable post birth) *Printed*

[Add additional lines for additional children born from this pregnancy]

Mother Full Name *(Printed)*	Signature	Date

[Authorization Author: Include for Clinical Trials Only]

Healthcare Provider (Investigator) Full Name *(Printed)* (If applicable)	Signature	Date

Study Number: _____ Site Number: _____

Subject Number: _____

[Authorization Author: Please add contact details for forwarding the signed authorization and if applicable for questions]

INITIAL PREGNANCY QUESTIONNAIRE (MOTHER)

You may return completed form to Amgen Office Fax or Email:

[Office Fax or Email]

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Health Care Professional ☐ Other_____ Parent exposed to product? ☐ Mother ☐ Father

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

*Did the patient sign the *Authorization for Release of Pregnancy Related Medical Information*? ☐ Yes ☐ No

Section 2 – Mother Current Pregnancy Information

Mother's Initials:

_____

Date of birth: (if permitted to provide by local laws)

_____
Day Month Year

Date of last menstrual period:

_____
Day Month Year

Age: _____ years

Number of fetuses_____

Estimated date of delivery:

_____
Day Month Year

Relevant Laboratory Tests & Procedures

Test Name	Test Date (dd/mm/yr)	Test Result

Section 3 – Mother Prenatal Medication History

Please list all medications (prescription and over-the-counter [include vitamins, herbal medications, etc.) and vaccines, taken by the **mother within 3 months prior to or during pregnancy**.

Amgen Product Used	Dose	Route (e.g. oral, subq)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Weeks of Pregnancy When Drug Taken (e.g. wk 28–wk 32)	Indication for Treatment
Resumed (if applicable)							
Amgen Product Lot Number _____ ☐ Lot Number Not Known							

List any other medications used within 3 months prior to or during the pregnancy

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

INITIAL PREGNANCY QUESTIONNAIRE (MOTHER) *continued*

Section 4 – Pregnancy Complication and Adverse Event Information

If the **mother** experienced any pregnancy complications (e.g. preeclampsia, gestational diabetes, placenta previa, etc.) please complete the following:

Pregnancy Complication or Adverse Event	**Date the Complication or Event Started** (dd/mm/yy)	**Date the Complication or Event Resolved** (dd/mm/yr)	**Outcome** (for example: resolved, not resolved, unknown, other, etc.)

Section 5 – Mother Relevant Medical History

Please provide pertinent medical history:

☐ hypertension ☐ seizure ☐ diabetes ☐ difficulty conceiving ☐ asthma ☐ thyroid dysfunction ☐ other_____

Please describe any additional factors that may have an impact on the outcome of this pregnancy, including relevant medical or family history, mother's occupation, illnesses during pregnancy etc. Please specify other disorders including familial birth defects/genetic/chromosomal disorders, etc.:

Section 6 – Mother Previous Obstetrical (Pregnancy) History

Please provide the number of pregnancies after treatment with an Amgen product was initiated. Include the pregnancy outcome for each of these pregnancies and any additional relevant details:

Number of pregnancies and outcome details:

☐ Normal healthy baby: _____

☐ Stillbirth: _____

☐ Baby with birth defect: _____

☐ Outcome unknown: _____

_____

☐ Miscarriage: _____

☐ Abortion (induced for medical reason): _____

_____

_____

☐ Abortion (induced for non-medical [voluntary] reason):

_____

☐ Other (specify outcome) or any significant additional information:

INITIAL PREGNANCY QUESTIONNAIRE (MOTHER) *continued*

Section 7 – Mother Current Pregnancy Outcome (if applicable)

Date pregnancy ended: _____
Day Month Year

Weeks of pregnancy at delivery (or if the outcome was a loss of pregnancy): _____ weeks

Pregnancy Outcome (check the appropriate box below):

☐ Live birth
☐ Number of infants_____(1: single, 2: twins, etc.)
(If multiple births: Please provide all information for each infant in the additional information text box below:)

If live birth: Gender: ☐ Male ☐ Female

Length: _____ cm/inches Birth weight: _____ gram/lb

Head circumference: _____cm/inches

Did the baby have any complications/medical problems/ congenital anomalies (birth defects)? ☐ Yes ☐ No
If yes, please provide specific information on the medical problem:

☐ Pregnancy loss (miscarriage)
☐ Stillbirth
☐ Termination
☐ Due to health issue (mother or baby)
☐ For voluntary reason
☐ Other (please specify):_____

_____

Please confirm if there were there any tests done or results given for the baby/fetus? ☐ Yes ☐ No
If yes, please provide the details below.

Additional Information on pregnancy outcome and/or test/results:

Section 8 – Reporter Signature (can be digital or manual)

Signature of person completing questionnaire: _____ Date: _____
Please print name: _____
Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your and your child's HCPs.
May Amgen contact your HCP? ☐ Yes ☐ No

Health Care Provider for the pregnancy/delivery:
Name _____ Phone ( ) _____ Fax ( ) _____
Email _____Address _____ City _____
State/Province _____ Zip/Postal Code _____

Health Care Provider who is prescribing the Amgen product:
Name _____ Phone ( ) _____ Fax ( ) _____
Email _____Address _____ City _____
State/Province _____ Zip/Postal Code _____

Health Care Provider for the child:
Name _____ Phone ( ) _____ Fax ( ) _____
Email _____Address _____ City _____
State/Province _____ Zip/Postal Code _____ Country _____

INITIAL PREGNANCY (FATHER) AUTHORIZATION AND QUESTIONNAIRE

From: {Title} {First Name} {Last Name} {Company Name} {Country}	[today]
To:[reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact]	

Event: Pregnancy	**Product**: [product_name]:[1]
AER#: [case_id]	**Reply Due By**: {Due Date}

Dear [reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact],

Thank you for reporting that your [patient_initials] female partner became pregnant while [product_name:first_suspect] ([generic_name:first_suspect]) therapy. Please send the completed questionnaire and signed consent form with requested information to the address, email or fax below.

Kindly note the following attachments:

- **AUTHORIZATION FOR RELEASE OF BIOLOGICAL FATHER AND INFANT HEALTH INFORMATION**
- **INITIAL PREGNANCY QUESTIONNAIRE (FATHER)**

Respectfully Yours,

{Title} {First Name} {Last Name}
{Company Name} {Country}
Email: {email}
Fax: {fax}
Phone: {phone}

Authorization for Release of Personal and Infant Health Information

[This is an example of text that can be used to obtain authorization for release of information from a male whose partner became pregnant or was already pregnant when he initiated an Amgen investigational or marketed product.]

Make alterations as directed within each square bracket [ ] that are appropriate to the region/country of jurisdiction. This text should be altered only if required by local laws and regulations and following legal review. Discard all directions in the final form, including this one, before sending externally.]

Male Authorization Form to Obtain Biological Father and Infant Health Information

[Authorization Author: Specify appropriate Amgen entity, e.g., Amgen Inc., Amgen Ltd., Amgen Canada] has been informed that your partner has become pregnant, or was already pregnant during your treatment with ***[add Amgen investigational or marketed product name.]***

Amgen Inc. and its respective global subsidiaries and affiliates (collectively referred to as "Amgen") collects father and infant (if applicable) health information when a man fathers a child or initiates treatment with an Amgen investigational or marketed drug product during his partner's pregnancy. The information collected will contribute to the body of knowledge that could ultimately help men and their health care providers (HCP) make more informed decisions about taking an Amgen medication during their partner's pregnancy or fathering a child while taking an Amgen medication.

We would like to collect this information whether or not you and your partner decide, in consultation with your or your partner's HCP(s), to continue with this pregnancy. With your partner's authorization, Amgen would also request to obtain her pregnancy related health information. Although Amgen collects information about your health, your partner's pregnancy related health, and the birth outcome, Amgen will not be responsible for any expenses relating to this pregnancy or its outcome. We do not provide any payment or compensation to you for providing information and there are no medications or treatments prescribed.

Because we are collecting personal health information, you are required to <<sign an authorization ***[for regions where signed authorization is required or]*** <<provide authorization>> ***[for regions where verbal authorization may be acceptable such as the U.S.]*** for release of health related information regarding your health and that of your child(ren). The medical information requested may include:

- your current health and the health of any children your previously fathered
- health information regarding your child(ren)'s born from this pregnancy (e.g., any newborn complications) up to 12 months following birth, if applicable.

[Authorization Author: Use this language if follow-up will only be conducted with the HCP]

If you agree to allow the collection of your and your child(ren)'s health information, Amgen will contact your HCP, and/or a study doctor (if your partner's pregnancy occurred during a clinical study), to request your health information. If applicable, additional information will be requested approximately 6 to 8 weeks after the estimated delivery date and when the child(ren) is/are 6 and 12

months of age. Your HCP may also contact other HCPs responsible for your or your child(ren)'s medical care to obtain additional information about your health and the health of your child(ren).

OR

[*Authorization Author*: Use this language if (acceptable per local laws and customs) follow-up may be conducted with the HCP and/or the patient (such as the US)]

If you agree to allow the collection of your and your child(ren)'s health information, Amgen will contact you and/or your HCP, or a study doctor (if your partner's pregnancy occurred during a study), to request your health information and the health of your child(ren). Amgen may also contact other HCPs responsible for your or your child(ren)'s medical care to obtain additional information about your health and the health of your child(ren). Contact information (name, phone number, etc.) about you and your child(ren) are not collected unless you have contacted Amgen or given authorization for Amgen to contact you directly. In that case, Amgen will continue to store your contact information. However, your personal identifiable information will not be released to any outside agencies unless required by law.

[*Authorization Author*: Include this language for all patients/subjects]

Because Amgen's medications may be taken by patients throughout the world, Amgen and its service providers have offices in many global locations. Other countries may not provide the same level of protection for your and your child(ren)'s personal information as is available in ***[patient's home country name]***. Regardless of the country in which the data is collected and processed, Amgen maintains administrative, technical and physical safeguards to protect information about you and your child(ren).

Regulatory agencies and business partners who distribute **[*add Amgen investigational or marketed product name*]** both within and outside ***[patient's home country name] [Authorization Author: Only include the Institutional Review Board and Ethics Committee information if father of the child was enrolled in a study]*** and the ***[specify appropriate name for the party responsible for ethics review and approval e.g., Institutional Review Board (IRB), Ethics Committee]*** may review your and your child(ren)'s health information that Amgen collects. If you have provided your and/or your child(ren)'s name and any other identifying data, this information will not be revealed, unless required by applicable law or regulation.

The information collected may also be used in future scientific research into **[*specify therapeutic area*]** and related scientific or educational publications. Neither you nor your child(ren) will be identified in any such publications.

Your authorization to provide this information is completely voluntary and gives Amgen and its trusted service provider's permission to obtain, store, and analyse information about you and your child(ren). You are free to withdraw your authorization at any time. **[*The following sentence may be used, depending on applicable laws and regulations for your country/region*].** You may also access information held about you and your child(ren), and you have the right to correct inaccuracies in the information held about you and your child(ren). If you withdraw your authorization, all information capable of identifying you or your child(ren) will be deleted from Amgen's database. Amgen may continue to use such anonymized information collected prior to the date of withdrawal. **[*The following may be used, depending on applicable laws and regulations for your country/region*]** In such

circumstances, since the data can no longer be linked to you, we will be unable to respond to access requests.

If you have any questions at any time, or you wish to withdraw your authorization, or you wish to exercise any rights you have with respect to information collected by Amgen (including on behalf of your child(ren), please write to Amgen (contact details given below).

Thank you for your willingness to provide Amgen with this important information.

By signing this authorization form, I confirm that I understand the terms above and agree to allow the collection of my and my child(ren)'s personal medical information.

Father's Full Name *(Printed)* Signature Date

Authorization on Behalf of Child

By signing this authorization form, I confirm that I agree that my child(ren) (born from this pregnancy) will take part in this activity and is/are subject to the same terms described above.

Child's Full Name (as applicable post birth) *Printed*

[Add additional lines for additional children resulting from this pregnancy]

Father's Full Name (Printer Signature Date

[Authorization Author: Include for Clinical Trials Only]

Healthcare Provider (Investigator) Full Name *(Printed)* (If applicable) Signature Date

Study Number _____ Site Number _____

Subject Number: _____

[Authorization Author: Please add contact details for forwarding the signed authorization and if applicable for questions]

INITIAL PREGNANCY QUESTIONNAIRE (FATHER)

You may return completed form to Amgen Office Fax or Email:

Section 1 – Reporter Information

Reporter: ☐ Father ☐ Health Care Professional ☐ Other _____

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

*Did the father sign the *Authorization for Release of Medical Information*? ☐ Yes ☐ No

Section 2 – Father Medication Information

Amgen Product Used	**Dose**	**Route** (e.g. oral, subq)	**Frequency** (e.g. daily, weekly)	**Date Drug Started** (dd/mm/yy)	**Date Drug Stopped** (dd/mm/yy)	**Indication for Treatment**
Resumed (if applicable)						
Amgen Product Lot Number _____ ☐ Lot Number Not Known						

Father's initials: _____

Age: _____

Father's pertinent medical history (cardiac conditions, rheumatoid arthritis, cancer, hypertension, etc.): _____

Section 3 – Current Pregnancy Outcome (for Live Birth)

☐ Number of infants_____(1: single, 2: twins, etc.)

Multiple births: Please provide all information for each multiple birth infant in the additional information text box below*:

Gender: ☐ Male ☐ Female Birth weight: _____gram/lb

Length: _____cm/inches Head circumference: _____cm/inches

Did the baby have any complications/medical problems/ congenital anomalies (birth defects)? ☐ Yes ☐ No

If yes, please provide specific information on the medical problem*:* *Additional information on pregnancy outcome:

Section 4 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name:_____

Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your and your child's HCPs.
May Amgen contact your HCP? ☐ Yes ☐ No

Health Care Provider who is prescribing the Amgen product:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____

Health Care Provider for the Child:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER)

From: {Title} {First Name} {Last Name} {Company Name} {Country}	[today]
To:[reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact]	

Event: Pregnancy	**Product**: [product_name]:[1]
AER#: [case_id]	**Reply Due By**: {Due Date}

Dear [reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact],

Thank you for reporting your [patient_initials] pregnancy while on [product_name:first_suspect] ([generic_name:first_suspect]) therapy. Please send the completed questionnaire with requested information to the address, email or fax below.

Kindly note the following attachments:

- **6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER)**

Respectfully Yours,

{Title} {First Name} {Last Name}
{Company Name} {Country}
Email: {email}
Fax: {fax}
Phone: {phone}

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER)

You may return completed form to Amgen Office Fax or Email:

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Health Care Professional ☐ Other _____

Any change in the reporter contact information? ☐ Yes ☐ No If yes, please provide updated contact information:

Name _____Phone ( ) _____Fax ( ) _____

Email _____ Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

Section 2 – Mother Prenatal Medication History

Please provide any additional medication information for medicines used during your pregnancy not previously reported. For example, if you resumed or discontinued the Amgen Product or any other medications during the pregnancy (include vitamins, folic acid, herbal medications, and vaccines).

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Section 3 – Mother Pregnancy Complications and/or Adverse Event Information Not Previously Reported

Pregnancy Complication or Adverse Event (e.g. preeclampsia, gestation diabetes)	Date the Complication or Event Started (dd/mm/yy)	Date the Complication or Event Resolved (dd/mm/yr)	Outcome (for example: resolved, not resolved, unknown, other, etc.)

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER) *continued*

Section 4 – Mother Current Pregnancy Outcome (if applicable)

Date pregnancy ended: _____
Day Month Year

Weeks of pregnancy at delivery (or if the outcome was a loss of pregnancy): _____ weeks

Pregnancy Outcome (please check the appropriate box below)

☐ Live birth
  ☐ Number of infants_____(1: single, 2: twins, etc.)
  (If multiple births: Please provide all information for each infant in the additional information text box below:)

☐ Pregnancy loss (miscarriage)
☐ Stillbirth
☐ Termination
  ☐ Due to health issue (mother or baby)
  ☐ For voluntary reason
  ☐ Other (please specify):_____

If live birth: Gender: ☐ Male ☐ Female

Length: _____cm/inches Birth weight: _____gram/lb Head circumference: _____cm/inches

Did the baby have any complications/medical problems/congenital anomalies (birth defects)? ☐ Yes ☐ No
If yes, please provide specific information below.

Additional Information on pregnancy outcome:

Section 5 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name: _____

Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your and your child's HCPs
May Amgen contact your HCP? ☐ Yes ☐ No

Health Care Provider for the pregnancy/delivery:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

Health Care Provider who is prescribing the Amgen product:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

Health Care Provider for the child:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (FATHER)

From: {Title} {First Name} {Last Name} {Company Name} {Country}	[today]
To:[reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact]	

Event: Pregnancy	**Product**: [product_name]:[1]
AER#: [case_id]	**Reply Due By**: {Due Date}

Dear [reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact],

Thank you for reporting that your [patient_initials] female partner became pregnant while on [product_name:first_suspect] ([generic_name:first_suspect]) therapy. Please send the completed questionnarie with requested information to the address, email or fax below.

Kindly note the following attachments:

- **6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (FATHER)**

Respectfully Yours,

{Title} {First Name} {Last Name}
{Company Name} {Country}
Email: {email}
Fax: {fax}
Phone: {phone}

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (FATHER)

You may return completed form to Amgen Office Fax or Email:

Section 1 – Reporter Information

Reporter: ☐ Father ☐ Health Care Professional ☐ Other_____

Any change in the reporter contact information? ☐ Yes ☐ No If yes, please provide updated contact information:

Name _____Phone ( ) _____Fax ( ) _____

Email _____ Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

Section 2 – Father Medication History

If you have changed the dose, frequency of the Amgen product you are taking during your partner's pregnancy, please provide this information below.

Amgen Medications	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment
Resumed, if applicable						

Section 3 – Current Pregnancy Outcome (for Live Birth)

☐ Number of infants_____(1: single, 2: twins, etc.)
Multiple births: Please provide all information for each multiple birth infant in the additional information text box below*:

Gender: ☐ Male ☐ Female Birth weight: _____gram/lb

Length: _____cm/inches Head circumference: _____cm/inches

Did the baby have any complications/medical problems/ congenital anomalies (birth defects)? ☐ Yes ☐ No

If yes, please provide specific information on the medical problem:

*Additional multiple birth information:

Section 4 – Reporter Signature

Signature of person completing questionnaire: _____Date: _____

Please print name: _____

Title: _____

Mother Safety Database #	
Infant Safety Database #	

SIX AND TWELVE MONTH INFANT QUESTIONNAIRE

From: {Title} {First Name} {Last Name} {Company Name} {Country}	[today]
To:[reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact]	

Event: Pregnancy	**Product**: [product_name]:[1]
AER#: [case_id]	**Reply Due By**: {Due Date}

Dear [reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact],

Thank you for reporting your [patient_initials] pregnancy while on [product_name:first_suspect] ([generic_name:first_suspect]) therapy. Please send the completed questionnaire with requested information to the address, email or fax below.

Kindly note the following attachments:

- **SIX AND TWELVE MONTH INFANT QUESTIONNAIRE**

Respectfully Yours,

{Title} {First Name} {Last Name}
{Company Name} {Country}
Email: {email}
Fax: {fax}
Phone: {phone}

Mother Safety Database # _____

Infant Safety Database # _____

AMGEN

SIX AND TWELVE MONTH INFANT QUESTIONNAIRE

You may return completed form to Amgen Office Fax or Email:

_____

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Father ☐ Health Care Professional (HCP) ☐ Other_____

Section 2 – Infant Healthcare Provider (HCP) Information

May Amgen contact the HCP for medical information regarding your child? ☐ Yes ☐ No

If yes, please provide contact information:

Name _____ Phone ( ) _____Fax ( ) _____

Email _____ Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

Section 3 – Infant Medical Health Information

List any other medications/drugs (include vitamins and over-the-counter medications taken by the child)

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Has the infant had any abnormal screening tests? ☐ Yes ☐ No If yes, please explain:

Has the infant followed growth curves and developmental milestones as expected for chronological age?

☐ Yes ☐ No If no, please explain:

Has the infant had any illnesses or persistent health problems? ☐ Yes ☐ No If yes, please explain:

Section 4 – Reporter Signature

Signature of person completing questionnaire: _____Date: _____

Please print name: _____Title and specialty if HCP_____

LACTATION AUTHORIZATION AND QUESTIONNAIRE

From: {Title} {First Name} {Last Name} {Company Name} {Country}	{Date}
To:	

Event: Pregnancy	**Product**: {Amgen Product}
AER#:	**Reply Due By**: {Due Date}

Dear ,

Thank you for reporting your (patient's) breastfeeding while on (Amgen Product) therapy. Please send the completed questionnaire and signed consent form with requested information to the address, email or fax below.

Kindly note the following attachments:

- **AUTHORIZATION FOR RELEASE OF BREASTFEEDING AND INFANT HEALTH INFORMATION**
- **LACTATION QUESTIONNAIRE**

Respectfully Yours,

{Title} {First Name} {Last Name}
{Company Name} {Country}
Email: {email}
Fax: {fax}
Phone: {phone}

Authorization for Release of Breastfeeding and Infant Health Information

This is an example of text that can be used to obtain authorization for release of information from a female who is breast feeding her child(ren) while taking an Amgen investigational or marketed product.

Make alterations as directed within each square bracket [ ] that are appropriate to the region/country. This text should be altered only if required by local laws and regulations and following legal review. Discard all directions in the form, including this one, before sending externally.

Lactation Authorization Form to Obtain Breastfeeding and Infant Health Information

[*Authorization Author: specify appropriate Amgen entity, e.g., Amgen Inc., Amgen Ltd., Amgen Canada*] has been informed that you are/were breastfeeding while taking **[name of Amgen investigational or marketed product name].**

Amgen Inc. and its respective global subsidiaries and affiliates (collectively referred to as "Amgen") collects health related information about women who are breastfeeding while taking an Amgen investigational or marketed drug product and about the child(ren) being breastfed. The information collected will contribute to the body of knowledge that could ultimately help mothers and their healthcare providers (HCP) make more informed decisions about taking an Amgen medication while breastfeeding.

Although Amgen collects information about you and your child(ren)'s health, Amgen will not be responsible for any expenses associated with your breastfeeding or your child(ren). We do not provide any payment or compensation to you for providing information and there are no medications or treatments prescribed.

Because we are collecting personal health information, you are required to **<<**sign an authorization>> ***[for regions where signed authorization is required or]*** **<<**provide authorization>> ***[for regions where verbal authorization may be acceptable such as the U.S.]*** for release of information concerning your health and that of your child(ren)'s. If you agree to provide this information, you and your child(ren) will be followed through your child(ren)'s first birthday. Collection of information may stop earlier if you discontinue breastfeeding or stop taking the Amgen drug prior to your child(ren)'s first birthday.

[Authorization Author: Use this language if follow-up will only be conducted with the HCP]
If you agree to be a part of this breastfeeding follow-up activity, Amgen will contact your HCP, to request your and your child(ren)'s health information. If you continue to take the Amgen product while breastfeeding, additional information will be requested when your child(ren) is 6 and 12 months of age. Your HCP may also contact other HCPs responsible for your or your child(ren)'s medical care to obtain additional information about your health and the health of your child(ren).

OR

[*Authorization Author*: ***Use this language if (acceptable per local laws and customs) follow-up may be conducted with the HCP and/or the patient (such as the US)***]
If you agree to be a part of this breastfeeding follow-up activity, Amgen will contact you, and/or your HCP to request your and your child(ren)'s health information. If needed, Amgen may also contact other HCPs responsible for your or your child(ren)'s medical care to obtain additional information about your health and that of your child(ren). Contact information (name, phone number, etc.) about you and your child(ren) is not collected unless you have contacted Amgen or given authorization for Amgen to contact you directly. In that case, Amgen will continue to store your contact information. However, your personal identifiable information will not be released to any outside agencies unless required by law.

[*Authorization Author*: **Include this language for all patients/subjects]**

Because Amgen's medications may be taken by patients throughout the world, Amgen and its service providers have offices in many global locations. Other countries may not provide the same level of protection for your and your child(ren)'s personal information as is available in ***[patient's home country name***]. Regardless of the country in which the data is collected and processed, Amgen maintains administrative, technical and physical safeguards to protect information about you and your child(ren).

Regulatory agencies and Amgen business partners who distribute [*add Amgen investigational or marketed product name*] both within and outside ***[patient's home country name]*** << [***Authorization Author: Only include the Institutional Review Board and Ethics Committee information if the patient was enrolled in a study***] and the ***[specify appropriate name for the party responsible for ethics review and approval e.g., Institutional Review Board (IRB), Ethics Committee]*** may review the pregnancy and infant health information that Amgen collects. If you have provided your and your child(ren)'s name and any other identifying data, this information will not be revealed, unless required by applicable law or regulation.

The information collected may also be used in future scientific research into **[*specify therapeutic area*]** and any related scientific or educational publications. Neither you nor your child(ren) will be identified in any such publications.

Your authorization to provide this information is completely voluntary and gives Amgen and its trusted service provider's permission to obtain, store, and analyze information about you and your child(ren). You are free to withdraw authorization at any time. **[*The following sentence may be used, depending on applicable laws and regulations for your country/region*]:** You may also access information held about you and your child(ren), and you have the right to correct inaccuracies in the information held about you and your child(ren). If you withdraw your authorization, all information capable of identifying you or your child(ren) will be deleted from Amgen's database. Amgen may continue to use such anonymized information collected prior to the date of withdrawal. **[*The following may be used, depending on applicable laws and regulations for your country/region*]** In such circumstances, since the data can no longer be linked to you, we will be unable to respond to access

requests.

If you have any questions at any time, or you wish to withdraw your authorization, or you wish to exercise any rights you have with respect to information collected by Amgen, including on behalf of your child(ren), please notify your doctor or write to Amgen (contact details given below).

Thank you for your willingness to provide Amgen this with important information.

By signing this authorization form, I confirm that I understand the terms above and agree to allow the collection of my and my child(ren)'s personal health information.

_____ _____ _____

Mother's Full Name (Printed) Signature Date

Authorization on Behalf of Child

By signing this authorization form, I confirm that I agree that my child(ren) will take part in this activity and is/are subject to the same terms described above.

_____

Child's Full Name (as applicable post birth) *Printed*

[Add additional lines for additional children resulting from this pregnancy]

_____ _____ _____

Mother's Full Name (Printed) Signature Date

[Authorization Author: Include for Clinical Trials Only]

_____ _____ _____

Healthcare Provider (Investigator) Full Name *(Printed)* Signature Date

Study Number _____ Site Number _____

Subject Number: _____

[Authorization Author: Please add contact details for forwarding the signed authorization and if applicable for questions]

AMGEN

Mother Safety Database #

Infant Safety Database #

LACTATION QUESTIONNAIRE

You may return completed form to Amgen Office Fax or Email:

Section 1 – Reporter Information

Reporter: ☐ Patient ☐ Health Care Professional (HCP) ☐ Other_____

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

*Did the patient sign the Authorization for Release of Medical Information? ☐ Yes ☐ No

Section 2 – Mother Demographic Information

Mother's initials: _____ **Age:** _____ **Date of birth** (if permitted by local laws): _____

Day Month Year

Section 3 – Mother Medication Information

Amgen Product Used While Breastfeeding	Dose	Route (e.g. oral, subcutan.)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment
Amgen Product Lot Number _____ ☐ Lot Number Not Known						

List any other medications/drugs (include vitamins, herbals, and vaccines) the Mother used while breastfeeding

Medications/Drugs	Dose	Route (e.g. oral, subcutan.)	Frequency (e.g. daily, weekly	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Section 4 – Mother's Medical Information

Mother's pertinent medical information (e.g. arthritis, hypertension, thyroid dysfunction, etc.):

Is the mother continuing to take an Amgen product while continuing to breastfeed? ☐ Yes ☐ No

If no, please provide the date when the Amgen product was discontinued or the mother stopped breastfeeding:

_____

Day Month Year

LACTATION QUESTIONNAIRE *(continued)*

Section 5 – Infant Medical Information

Does the infant currently have any health issues? ☐ Yes ☐ No

If yes, please provide current health details and treatment provided:

Is the infant gaining weight and developing normally? ☐ Yes ☐ No If no, please specify:

Section 6 – Infant Medication Information

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Section 7 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name: _____ Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your child's HCP
May Amgen contact your child's HCP? ☐ Yes ☐ No

Health Care Provider for the child:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

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 Date of Birth:** mm_____ / dd_____/ yyyy_____

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:** _____

****

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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 DOB:** mm_____ / dd_____/ yyyy_____

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 LMP mm_____ / dd_____/ yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____/ yyyy_____ ☐ Unknown ☐ N/A

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:** _____

****

Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)

Approved key messages of the additional risk minimization measures

- **Managed Distribution Program:**
  - To manage the product supply chain to ensure that cold storage requirements are observed (-90°C to -70°C)
  - To control distribution to medical centers which commit to:
    - trained HCPs to minimize the risk of specified adverse drug reactions in HCPs, patients, and close contacts of patients
    - train HCPs and support personnel regarding safe and appropriate storage, handling, and administration, and clinical follow-up for patients
    - provide specified safety information to patients and communicate to patients the importance of sharing this information with family and caregivers
    - trained HCPs to record batch number information in patients' charts for all injections and to provide the batch number when reporting adverse drug reactions
- **Physician Education Booklet:**
  - To inform HCPs about important risks associated with Imlygic (disseminated herpetic infection, potential harm to the fetus or neonate in pregnancy, herpetic infection in Imlygic-treated patients, and accidental exposure of close contacts and HCPs to Imlygic).
- **Patient Safety Brochure:**
  - To provide important safety information for patients, including information patients can share with family, caregivers, and close contacts, and information on the risks of transmission of Imlygic, disseminated herpetic infection, and serious infection in immunocompromised individuals.
- **Patient Alert Card:**
  - Intended for the patient to present to HCPs upon consultation or hospitalization and informs that the holder has been treated with Imlygic.

Annex 7. Other Supporting Data (Including Referenced Material)

Table of Contents

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Talimogene Laherparepvec qPCR Assay and Validation Summaries

1.1 Method Description of Qualitative and Quantitative Real Time Polymerase Chain Reaction Assay for Detection of Talimogene Laherparepvec in Whole Blood, Swabs, and Urine

Introduction

The talimogene laherparepvec virus is a genetically engineered virus using a HSV-1 clinical isolate (JS1) as the backbone. The neurovirulence factor ICP34.5 gene which is present as 2 copies in JS1 has been deleted and replaced with a cassette that includes the CMV immediate-early promoter, human GM-CSF coding sequence and a bovine growth hormone polyA sequence. The removal of the ICP34.5 gene makes the virus more specific for replication in tumor cells. The cassette that produces human GM-CSF results in increased recruitment of host immune cells to the tumor site.

To quantitatively and qualitatively detect talimogene laherparepvec virus in human subject, a quantitative qPCR assay with qualitative cut-point was fully developed and validated at Viracor IBT lab.

Method descriptions

For qPCR method:

The methodology for a real time qPCR assay was fully developed and validated for the amplification and detection of the talimogene laherparepvec gene in blood, urine and swab sample. The assay employs primers (in Table 38) specific to talimogene laherparepvec gene sequences. The method is comprised of several steps including nucleic acid extraction, nucleic acid amplification and detection, and total nucleic acid quantification.

Nucleic acid extraction

Nucleic acid extraction is performed following instructions in SOP NucliSens easyMAG Total Nucleic Acid Extraction standard protocol. The sample input volume is 500 µL with an elution output volume of 100 µL. Nucleic acid extraction for whole blood specimens is performed following instructions in SOP QIAamp DNA Mini and DNA Blood Mini Extractions protocol.

Nucleic acid amplification and detection

Nucleic acid amplification is performed as following instruction in SOP Real-Time PCR and RT-PCR Using ABI 7500 SDS Instruments: the reaction wells of Applied Biosystems Inc. Fast plates contain 30 µL reactions with 15 µL ABI Fast Universal

2X Mix, 10 μL of template DNA, and 5 μL of primer probe mix for the talimogene laherparepvec PCR reaction.

The talimogene laherparepvec qPCR amplifies a target sequence from inside the GM-CSF cassette that is present in two copies per talimogene laherparepvec virus. The TaqMan probe for the assay is labeled with a FAM-MGB fluorophore and multiplexed with the UIC assay with a VIC-TAMRA labeled probe. A no template control (NTC) is included for each real-time qPCR plate to ensure the accuracy.

Total nucleic acid quantification

The total dsDNA concentration for each extracted sample is determined according to SOP BioTEK Epoch Operation, Maintenance, and Calibration. This data is then combined with the qPCR copies/reaction result to calculate copies/μg DNA as the final units for each sample.

Table 38. Oligonucleotide Sequences, Concentrations and Critical Components of the Talimogene Laherparepvec qPCR Assay

Oligonucleotide	oligonucleotide sequence 5' ---- 3'	Label	Final Concentration nM
ONCCOPYC Forward	GTACGGTGGGAGGTCTATATAAGCA		300
ONCCOPYC Reverse	AGTGAGTCGTATTAATTTCGATAAGCCA		600
ONCCOPYC Probe	CTGGCTAACTAGAGAACC	FAM-MGB	200
Internal Control Forward	CAGCAGAACACCCCCATC		200
Internal Control Reverse	GTGATCGCGCTTCTCGTT		200
Internal Control Probe	AACCACTACCTGAGCACCCAGTCC	VIC-TAMRA	200
Master mix Components			
Ambion BSA			0.9 μg/μL
ABI 2x Fast Taqman Master Mix			1X

The quantification sensitivity for qPCR: lower limit of quantification (LLOQ)

The LLOQ is defined as the lowest concentration at which ≥ 95% of the samples are predicted to be detected and the total analytical error (TAE) for accuracy is ≤ 1.0. The LLOQ are 24, 18, and 1.76 copies/ug DNA, for urine, swab, and blood samples, respectively.

Qualitative cut-off point or qualitative measurement

The cutoff Ct value is established for each respective specimen type as the Ct value of the C50 upper 95% confidence interval determined by Probit analysis, where C50 is the concentration at which 50% of samples will be detected and 50% of samples will not be detected, as described in the CLSI guideline EP12-A2. The Ct values of cut-off points are 37.8 (5.8 copies/ug DNA), 37.4 (7.5 copies/ug DNA), and 37.4 (0.6 copies/ug DNA) for urine, swab and blood sample, respectively.

1.2 Validation Summary of Qualitative and Quantitative Real Time Polymerase Chain Reaction Assay for Detection of Talimogene Laherparepvec in Whole Blood, Swabs, and Urine

Validation Report to Establish the Performance Characteristics of the Talimogene Laherparepvec Quantitative and Qualitative Real Time PCR (qPCR) Assay in Whole Blood, Swabs, and Urine

QPCR Assay Method Validation Summary

The qPCR method validation was performed at Viracor-IBT Laboratories, Inc. (1001 NW Technology Drive, Lee's Summit, MO 64086, USA).

The performance characteristics of the talimogene laherparepvec real time qPCR assay for whole blood, swab, and urine specimens meets the acceptance criteria as specified in the validation protocol, 21120.1989 Validation Protocol to Establish the Performance Characteristics of the Talimogene Laherparepvec Quantitative and Qualitative Real Time PCR (qPCR) Assay in Whole Blood, Swabs and Urine. Therefore, whole blood, swab, and urine specimens are accepted for Biopharma use for the talimogene laherparepvec PCR assay.

This validation experiments include the extraction methods using automated extraction platforms (QIAcube with Qiagen DNA Blood Mini Kit for whole blood and Biomerieux easyMAG instrument and reagents for swabs and urine), assessment of the performance characteristics for the talimogene laherparepvec qPCR assay: analytical sensitivity, analytical specificity, precision (reproducibility), diagnostic accuracy, linearity

and dynamic range and analyte stability and acceptance criteria for each of these parameters for the talimogene laherparepvec qPCR assay using TaqMan technology and ABI 7500 Fast instruments.

This validation was composed using guidelines recommended by the New York State Department of Health, CLIA, CAP, CLSI and the FDA Bioanalytical Method Validation.

Table 39 is a summary of the validation results including acceptance criteria.

Table 39. Summary of Validation Results for the Talimogene Laherparepvec qPCR Assay in Human Whole Blood, Swabs and Urine

Performance Characteristic	Acceptance Criteria	Validation Results	Pass/Fail
Analytical Specificity Reactivity (Inclusivity)	For reactivity, Ct must be $\leq$ 30 for talimogene laherparepvec stock.	The talimogene laherparepvec virus stock was detected at a Ct of 15.59.	**Pass**
Analytical Specificity Cross-reactivity	For cross-reactivity, no signal must be detected for nontarget nucleic acids.	All non-target nucleic acids, which were positive for their virus-specific qPCR assays with a Ct $<$ 30, were found to be "not detected" by the talimogene laherparepvec qPCR assay.	**Pass**
Linearity and Dynamic Range Amplification	Plot the Ct values versus the $\log_{10}$ copies/mL concentration values and determine the R^2 and the slope of the line generated by linear regression analysis. The qPCR assay was considered to demonstrate acceptable performance if the R^2 is $\geq$ 0.98, the slope is $\leq$ -3.64 and $\geq$ -3.19 and all samples are detected.	The PCR assay demonstrated acceptable performance with the $R^2 = 0.9976$, a slope = -3.353 and all samples were detected. The talimogene laherparepvec assay was linear over seven orders of magnitude. The assay standards ranged from $5x10^1$ talimogene laherparepvec copies/mL to $5x10^7$ talimogene laherparepvec copies/mL for swabs and urine and $6.25\ x10^1$ talimogene laherparepvec copies/mL to $6.25\ x10^7$ talimogene laherparepvec copies/mL for whole blood.	**Pass**
Linearity and Dynamic Range Full Process (Extraction and PCR)	Plot observed $\log_{10}$ copies/µg concentration values versus expected $\log_{10}$ copies/µg concentrations values and determine the coefficient of determination (R^2) for the regression analysis. The R^2 must be $\geq$ 0.95 and the slope must be 1.0 $\pm$ 0.15.	Swab: The R^2 was determined to be 0.9977, the Y-intercept was -0.1905 and the slope was 0.9944. Urine: The R^2 was determined to be 0.9896, the Y-intercept was 0.3144 and the slope was 1.037. Whole Blood: The R^2 was determined to be 0.9939, the Y-intercept was 0.2905 and the slope was 0.9652.	**Pass**

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Performance Characteristic	Acceptance Criteria	Validation Results	Pass/Fail
Assay Cut-off	The mean Ct value for the C50 upper 95% confidence interval was determined in each specimen type by Probit analysis, where C50 is the concentration at which 50% of the samples were detected and 50% of the samples will not be detected as described in the CLSI guideline EP12-A2.	Swab: 50% detection is predicted at 5.73 talimogene laherparepvec copies/μg (3.70 - 7.46 95% confidence interval) which corresponds to a Ct of 37.82 (38.45 - 37.44 95% confidence interval). Urine: 50% detection is predicted at 4.11 talimogene laherparepvec copies/μg (2.33 - 5.81 95% confidence interval) which corresponds to a Ct of 38.34 (39.15 - 37.84 95% confidence interval). Whole Blood: 50% detection is predicted at 0.41 talimogene laherparepvec copies/μg (0.18 - 0.58 95% confidence interval) which corresponds to a Ct of 37.88 (39.09 - 37.38 95% confidence interval).	**Pass**
Analytical Sensitivity Lower Limit of Quantification	The LLOQ is defined as the lowest level at which ≥ 95% of samples are predicted to be detected by probit analysis and at which the TAE for accuracy is ≤ 1.0.	Swab: 95% detection was seen at 19 talimogene laherparepvec copies/mL with a TAE of 0.55 or 18 talimogene laherparepvec copies/μg with a TAE of 0.60. Urine: 95% detection was seen at 24 talimogene laherparepvec copies/mL with a TAE of 0.79 or 24 talimogene laherparepvec copies/μg with a TAE of 0.77. Whole Blood: 95% detection was seen at 31 talimogene laherparepvec copies/mL with a TAE of 0.85 or 1.76 talimogene laherparepvec copies/μg with a TAE of 0.76.	**Pass**

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Performance Characteristic	Acceptance Criteria	Validation Results	Pass/Fail
Precision Intra-assay Reproducibility	The log_{10} copies/µg %CV for intra-assay precision at the low, medium and high concentrations for talimogene laherparepvec virus must be ≤ 7% for swabs and urine and ≤ 8% for whole blood. Negative samples must have UIC Ct values ≤ 35.	Swab: The log_{10} copies/µg %CV for intra-assay precision was 0.66 - 2.04%, 0.19 - 3.81% and 0.71 - 1.23% for low, medium and high concentrations, respectively. Urine: The log_{10} copies/µg %CV for intra-assay precision was 0.29 - 2.36%, 0.45 - 1.30% and 0.47 - 1.22% for low, medium and high concentrations, respectively. Whole Blood: The log_{10} copies/µg %CV for intra-assay precision was 2.46 - 4.16%, 1.23 - 2.51% and 1.48 - 2.88% for low, medium and high concentrations, respectively.	**Pass**
Precision Inter-assay Reproducibility	The log_{10} copies/µg %CV for inter-assay precision at the low, medium and high concentrations must be ≤ 8% for swabs and urine and ≤ 9% for whole blood. Negative samples must have UIC Ct values ≤ 35.	Swab: The log_{10} talimogene laherparepvec copies/µg %CV for inter-assay precision at the low, medium and high concentrations was 1.69%, 2.20% and 1.09%, respectively. Urine: The log_{10} talimogene laherparepvec copies/µg %CV for inter-assay precision at the low, medium and high concentrations was 1.70%, 1.17% and 1.04%, respectively. Whole Blood: The log_{10} talimogene laherparepvec copies/µg %CV for inter-assay precision at the low, medium and high concentrations was 5.50%, 4.55% and 3.62%, respectively.	**Pass**

Table 39. Summary of Validation Results for the Talimogene Laherparepvec qPCR Assay in Human Whole Blood, Swabs and Urine

Performance Characteristic	Acceptance Criteria	Validation Results	Pass/Fail
Accuracy	All positive samples must be identified as positive and all negative samples must be identified as negative for qualitative assessment. For quantitative assessment all samples must be ± 0.5 $\log_{10}$ copies/µg of the expected nominal value. Negative samples must have UIC Ct values ≤ 35.	Swab, Urine and Whole Blood: All positive samples were identified as positive and all negative samples were identified as negative. Additionally, for the quantitative assessment, all samples were ± 0.5 $\log_{10}$ copies/µg of the expected nominal value.	**Pass**
Analyte Stability – Short- and Long-term Storage	At each time point and storage condition being assessed, the results were considered to demonstrate acceptable stability if there is a decrease of ≤ 0.50 $\log_{10}$ copies/mL relative to the Time 0 data.	Swab: -80°C storage up to 90 days, refrigerated storage up to 4 days and ambient storage up to 4 days were shown to have acceptable stability. The ambient stability is still ongoing. Urine: -80°C storage up to 90 days and refrigerated storage up to 3 days were shown to have acceptable stability. Ambient storage was stable up to 4 hours. Whole Blood: -80°C storage up to 90 days, refrigerated storage up to 4 days and ambient storage up to 4 days were shown to have acceptable stability. Whole blood, swab and urine specimens were stable up to 7 days at -20°C storage.	**Pass**
Analyte Stability – Freeze-thaw	One through six freeze-thaw cycles were evaluated and the results were considered to have demonstrated acceptable stability if there is a decrease of ≤ 0.50 $\log_{10}$ copies/µg relative to the Time 0 data.	Swab, Urine and Whole Blood: Up to 6 freeze-thaw cycles were shown to have acceptable stability.	**Pass**

Annex 8. Summary of Changes to the Risk Management Plan Over Time

Table 40. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
1.2(W)	At the time of authorization Date of RMP: 04 November 2015 Date of approval: 16 December 2015 EMEA/H/C/00002771	**Safety Concerns:** Important Identified Risks: • Disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency) • Accidental exposure of HCP to talimogene laherparepvec • Obstructive airway disorder • Immune-mediated adverse reactions • Plasmacytoma at the injection site • Deep vein thrombosis • Cellulitis at site of injection Important Potential Risks: • Disseminated herpetic infection in immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents) • Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Symptomatic talimogene laherparepvec infection in non-tumor tissue in treated patients • Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients • Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection • Combination with other therapies like chemotherapy or immunosuppressive agents • Recombination of talimogene laherparepvec with wild-type HSV-1 virus may occur • Impaired wound healing at site of injection • Delayed next line treatment in non-responders

Table 40. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
1.2(W) (continued)		Important Potential Risks (continued): • Loss of efficacy in patients treated with systemic acyclovir for complications • Talimogene laherparepvec-mediated anti-GM-CSF antibody response Missing Information: • Additional clinical biodistribution and shedding data in melanoma • Pregnant and lactating women • Pediatric patients • Patients below the age of 40 years • Patients with renal or hepatic impairment • Treatment of patients with cardiac impairment • Patients of race or ethnic origin other than white • Long-term safety data • Long-term efficacy data • Treatment of patients with bone metastases • Treatment of patients with cerebral metastases • Treatment of patients with more than 3 visceral lesions • Treatment of patients with metastatic lesions greater than 3 cm • Treatment of patients with ocular melanoma • Treatment of patients with mucosal melanoma **Pharmacovigilance Plan:** Specific Adverse Drug Reaction Follow-up Forms: • Suspected IMLYGIC (Talimogene Laherparepvec) or Herpes Virus Associated Adverse Event • Clinical Trial or Postmarket Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact • Suspected IMLYGIC Autoimmune Adverse Event • Pregnancy and lactation follow-up forms

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Table 40. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
1.2(W) (continued)		Category 1 to 3 Studies: • Study 20120139 A registry study to evaluate the survival and long-term safety of subjects with melanoma who previously received talimogene laherparepvec. • Study 20130193 A postmarketing, prospective cohort study of patients treated with talimogene laherparepvec in clinical practice to characterize the risk of herpetic illness among patients, close contacts, and health care providers; and long-term safety in treated patients. • Study 20120324 A phase 2, multicenter, single-arm trial to evaluate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to IVM1c melanoma. • Study 20110261 A phase 1, open-label, dose de-escalation study to evaluate the tolerability, safety, and activity of talimogene laherparepvec in children from birth to < 18 years of age with melanoma or with advanced non-central nervous system tumors that are amenable to direct injection and for which no effective treatment is known. • Study Number: To be determined. A Randomized, controlled study to evaluate the safety and efficacy of talimogene laherparepvec in children from birth to < 18 years of age with a pediatric solid malignant tumor as part of a multi-modal treatment approach. **Postauthorization Efficacy Plan:** • Study 20120139 A registry study to evaluate the survival and long-term safety of subjects with melanoma who previously received talimogene laherparepvec. **Risk Minimization Measures:** • Physician Education Booklet • Managed distribution program • Patient safety brochure and patient alert card

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Version	Date of RMP Approval Date Procedure	Change
2.0	Date of RMP: 16 August 2016 Date of approval: 07 October 2016 EMEA/H/C/002771/ IB/0007	**Safety Concerns:** No changes **Pharmacovigilance Plan:** Due dates of Studies 20120324 and 20110261 were updated. **Postauthorization Efficacy Plan:** No change **Risk Minimization Measures:** No change
3.0	Date of RMP: 03 October 2017 Date of approval: 13 November 2017 EMEA/H/C/002771/ IB/0017	**Safety concerns:** No changes **Pharmacovigilance Plan:** Due date of final analysis clinical study report for Study 20120324 was updated. **Postauthorization Efficacy Plan:** No change **Risk Minimization Measures:** No change
4.0	Date of RMP: 10 September 2018 EMEA/H/C/002771/ II/0028	**Safety Concerns:** The following important identified risks were reclassified as not important and removed from the RMP: • Obstructive airway disorder • Plasmacytoma at the injection site • Deep vein thrombosis • Cellulitis at site of injection The following important potential risks were reclassified as not important and removed from the RMP: • Combination with other therapies like chemotherapy or immunosuppressive agents • Recombination of talimogene laherparepvec with wild-type HSV-1 virus may occur • Impaired wound healing at site of injection • Delayed next line treatment in non-responders • Loss of efficacy in patients treated with systemic acyclovir for complications

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Version	Date of RMP Approval Date Procedure	Change
4.0 (continued)		The following missing information was removed from the RMP: • Use in patients below the age of 40 years • Use in patients with renal or hepatic impairment • Treatment of patients with cardiac impairment • Use in patients of race or ethnic origin other than white • Treatment of patients with bone metastases • Treatment of patients with active cerebral metastases • Treatment of patients with more than 3 visceral lesions • Treatment of patients with metastatic lesions greater than 3 cm • Treatment of patients with ocular melanoma • Treatment of patients with mucosal melanoma **Pharmacovigilance Plan:** No change **Postauthorization Efficacy Plan:** • Study 20120139 was removed as a postauthorization efficacy study. **Risk Minimization Measures:** No change
5.0	Date of RMP: 15 November 2018 EMEA/H/C/002771/II/0029	**Safety Concerns:** The following missing information was removed from the RMP: • Additional clinical biodistribution and shedding data in melanoma **Pharmacovigilance Plan:** • Study 20120324 removed as study complete **Postauthorization Efficacy Plan:** No change **Risk Minimization Measures:** No change

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Version	Date of RMP Approval Date Procedure	Change
4.1	Date of RMP: 29 January 2019 EMEA/H/C/002771/ II/0028	**Safety Concerns:** The following safety concern was reclassified as an important potential risk and added to the RMP: • Combination with other therapies like chemotherapy or immunosuppressive agents The following safety concern was reclassified as missing information and added to the RMP: • Treatment of patients with metastatic lesions greater than 3 cm **Pharmacovigilance Plan:** No change **Postauthorization Efficacy Plan:** The following postauthorization efficacy studies were added to the RMP: • Study 20110265 • Study 20110266 **Risk Minimization Measures:** No change **Annexes:** • Annex 5: Protocols for Studies 20110265 and 20110266 were appended
5.1	Date of RMP: 15 February 2019 EMEA/H/C/002771/ II/0029	**Safety Concerns:** No change **Pharmacovigilance Plan:** No change **Postauthorization Efficacy Plan:** No change **Risk Minimization Measures:** No change **Annexes:** No change **Other Changes:** Information on detectable DNA from swabs of the exterior of occlusive dressings added to justification text for removal of the missing information 'Additional clinical biodistribution and shedding data in melanoma.'

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Version	Date of RMP Approval Date Procedure	Change
6.0	Date of RMP: 27 March 2019 Date of approval: 28 March 2019 EMEA/H/C/002771/ II/0028 EMEA/H/C/002771/ II/0029	**Safety Concerns:** No change **Pharmacovigilance Plan:** No change **Postauthorization Efficacy Plan:** No change **Risk Minimization Measures:** No change **Annexes:** No change **Other Changes:** Consolidation of EU RMP versions 4.1 and 5.1.
7.0	Date of RMP: 26 April 2019 EMEA/H/C/002771/II/0034	**Safety Concerns:** No change **Pharmacovigilance Plan:** The following studies were added to evaluate the effectiveness of additional risk minimization measures: • Study 20180062 • Study 20180099 **Postauthorization Efficacy Plan:** No change **Risk Minimization Measures:** • Plans to evaluate the effectiveness of the additional risk minimization measures were updated as follows: - Effectiveness of the managed distribution program will be measured by conducting an internal evaluation of managed distribution process metrics - Effectiveness of the Physician Education Booklet will be measured using a cross-sectional survey (Study 20180099) - Effectiveness of the patient safety brochure and patient alert card will be measured using a cross-sectional survey (Study 20180062) • Patient safety brochure and patient alert card removed as additional risk minimization measures for the important identified risk of accidental exposure of healthcare provider to talimogene laherparepvec and the important potential risk of immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection as these measures are not relevant for these risks.

Table 40. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
7.0 (continued)		**Annexes:** • Annex 2: Updated to include Studies 20180062 and 20180099 • Annex 3: Protocols for Studies 20180062 and 20180099 were appended
8.0	Date of RMP: 13 June 2019 EMEA/H/C/002771/ IB/0035	**Safety Concerns:** No change **Pharmacovigilance Plan:** No change **Postauthorization Efficacy Plan:** Clinical study report due date updated for Study 20110265. **Risk Minimization Measures:** No change **Annexes:** No change
8.1	Date of RMP: 15 July 2019 EMEA/H/C/002771/ IB/0035	**Safety Concerns:** No change **Pharmacovigilance Plan:** No change **Postauthorization Efficacy Plan:** No change **Risk Minimization Measures:** No change **Annexes:** No change **Other Changes:** Removal of all of EU RMP v7.0 changes (procedure EMEA/H/C/002771/II/0034) so that only v8.0/v8.1 changes (procedure EMEA/H/C/002771/IB/0035) are contained within the current EU RMP.

Table 40. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
9.0	Date of RMP: 06 August 2019 Approval: 19 September 2019 Procedure: EMEA/H/C/002771/II/0034	**Safety Concerns:** No change **Pharmacovigilance Plan:** The following studies were added to evaluate the effectiveness of additional risk minimization measures: • Study 20180062 • Study 20180099 **Postauthorization Efficacy Plan:** No change **Risk Minimization Measures:** • Plans to evaluate the effectiveness of the additional risk minimization measures were updated as follows: - Effectiveness of the managed distribution program will be measured by conducting an internal evaluation of managed distribution process metrics - Effectiveness of the Physician Education Booklet will be measured using a cross-sectional survey (Study 20180099) - Effectiveness of the patient safety brochure and patient alert card will be measured using a cross-sectional survey (Study 20180062) Patient safety brochure and patient alert card removed as additional risk minimization measures for the important identified risk of accidental exposure of healthcare provider to talimogene laherparepvec and the important potential risk of immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection as these measures are not relevant for these risks. **Annexes:** • Annex 2: Updated to include Studies 20180062 and 20180099 • Annex 3: Protocols for Studies 20180062 and 20180099 were appended

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Version	Date of RMP Approval Date Procedure	Change
9.1	Date of RMP: 12 June 2020 Approval Date: 13 July 2020 Procedure: EMEA/H/C/002771/ IB/0040	**Other Changes:** To extend the final report date for the category 3 Study 20180099 from 31 August 2020 to 28 February 2021
9.2	Date of RMP: 14 December 2020 Procedure: EMEA/H/C/002771/ IB/0042	**Other Changes:** To extend the final report date for the category 3 Study 20180062 from 31 March 2021 to March 2022
9.3	Date of RMP: 25 January 2021 Approval Date: 25 January 2021 Procedure: EMEA/H/C/002771/ IB/0042	**Other Changes:** To correct the status of the category 3 Studies 20130193, 20180062, and 20180099 from planned to ongoing.
10.0	Date of RMP: 18 August 2022 Procedure: EMEA/H/C/002771/ II/0059	**Safety Concerns:** The following safety concern was updated as the important identified risk of Disseminated Herpetic Infection: • Disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency) The following important potential risks were reclassified as an important identified risk an included it within the updated important identified risk of disseminated herpetic infection: • 'Disseminated herpetic infection in immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require chronic high-dose steroids or other immunosuppressive agents) • 'Symptomatic talimogene laherparepvec infection in non tumor tissue in treated patients'

Version	Date of RMP Approval Date Procedure	Change
10.0 (continued)		**Pharmacovigilance Plan:** The following Additional Pharmacovigilance Activities were removed: • Amgen will facilitate testing of GM-CSF antibodies for patients with reported adverse events' as a pharmacovigilance activity. • 'Study to be determined: A randomized, controlled study to evaluate the safety and efficacy of talimogene laherparepvec in children from birth to < 18 years of age with a pediatric solid malignant tumor as part of a multi-modal treatment approach.' Category 3. The following studies were removed additional risk minimization measures as they were completed: • Study 20180062 • Study 20180099 • Study 20120139 **Postauthorization Efficacy Plan:** Updated to remove Study 20110265 **Annexes:** • Annex 2: Updated to include Studies 20180062, 20180099, 20120139 • Annex 5: Updated to remove Study 20110265
10.1	Date of RMP: 03 March 2023 Procedure: EMEA/H/C/002771/II/0059	**Safety Concerns:** Updated the potential mechanism, severity, and frequency for the important identified risk 'Disseminated herpetic infection.' **Pharmacovigilance Plan:** Updated the milestone dates for the following studies: • Study 20130193 • Study 20110261 **Annexes:** • Annex 3: Updated to remove completed Studies 20180062, 20180099, and 20120139
10.2	Date of RMP: 12 April 2023 Approval Date: 26 April 2023 Procedure: EMEA/H/C/002771/II/0059	**Safety Concerns:** Updated the frequency of the important identified risk 'Disseminated herpetic infection'

Version	Date of RMP Approval Date Procedure	Change
11.0	Date of RMP: 26 May 2023 Procedure: EMEA/H/C/002771/II/0064	**Safety Concerns:** Removed the important potential risk 'Talimogene Laherparepvec-mediated Anti-GM-CSF Antibody Response' **Postauthorization Efficacy Plan:** Updated to remove Study 20110266 **Annexes:** • Annex 5: Updated to remove completed Study 20110266 • Annex 7: Updated to remove the validation studies related to the removed risk of 'Talimogene Laherparepvec-mediated Anti-GM-CSF Antibody Response'
11.1	Date of RMP: 19 September 2023 Procedure: EMEA/H/C/002771/II/0064	**Other Changes:** Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s): Updated 'Main Existing Treatment Options' to present the main treatment information