A phase II study using talimogene laherparepvec for inflammatory breast cancer or non-inflammatory breast cancer patients with inoperable local recurrence

Protocol 2014-0034

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Table of Contents

1.0 Objective

1.1 Primary objectives

To determine the efficacy of talimogene laherparepvec in inflammatory breast cancer or non-inflammatory breast cancer patients with inoperable local recurrence measured by the overall response rate

1.2 Secondary objectives

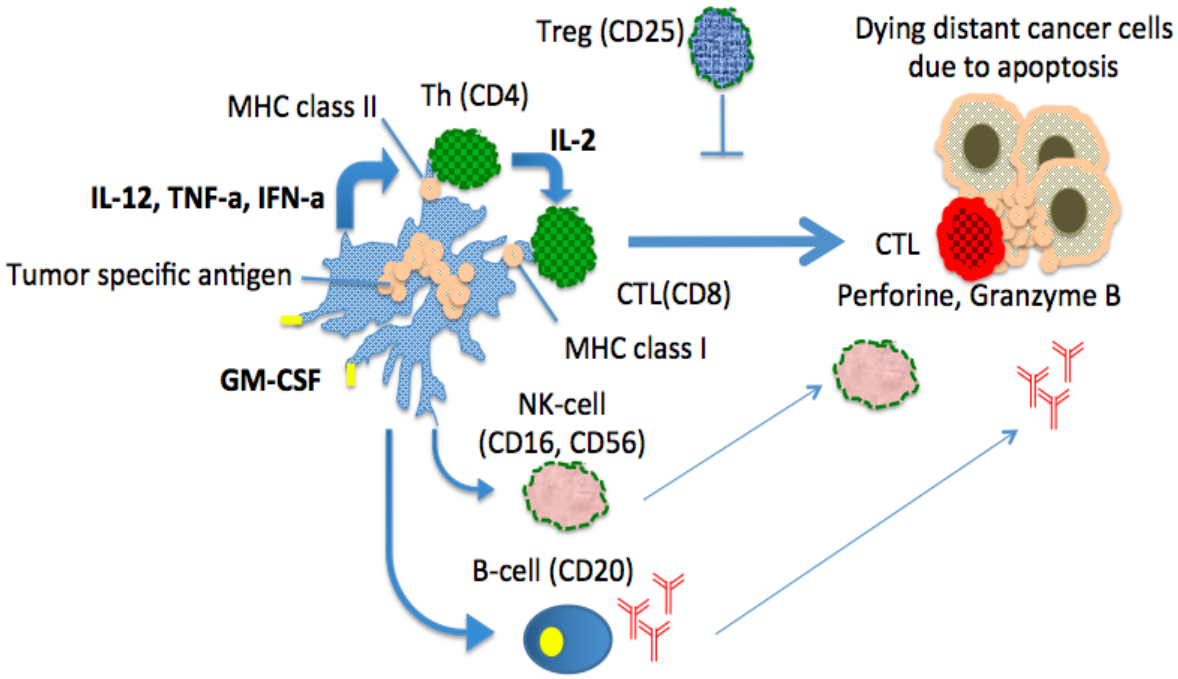
- To determine the efficacy of talimogene laherparepvec in inflammatory breast cancer or non-inflammatory breast cancer patients with inoperable local recurrence measured by the overall disease control rate
- To determine the rate of local overall response and disease control rate, progression-free survival (PFS), and overall survival (OS) in all patients.
- To determine the rate of local overall response and disease control rate, PFS, and OS in patients without distant metastases.
- To determine the rate of local overall response and dsease control rate, PFS, and OS in patients with distant metastases.
- To determine the safety of talimogene laherparepvec injection to local disease.

1.3 Correlative studies

- To determine the effect of talimogene laherparepvec on injection sites and distant metastatic sites by evaluating immune function and apoptosis with immune cell surface markers and cytokines. Talimogene laherparepvec induces systemic immune reaction through activation of dendritic cell, and enhance cellular immunity. Cytotoxic T-lymphocyte (CTL) is estimated to offense distant cancer cells via apoptosis mechanism and humoral immunity was not determined to involve in this systemic immunity. However, the activation of dendritic cells may subsequently activate NK-cells and B-cells. Other leukocyte such as neutrophil and monocyte are currently undetermined their function within systemic immune reaction induced by talimogene laherparepvec (Figure 1).
- To assess changes in the following:
    - Serum or plasma levels of interleukin (IL)-2, IL-12, tumor necrosis factor (TNF)-alpha (α), and interferon (IFN)- alpha (α); (Reuben's Lab)
    - Phenotype for T-cell subsets (CD3, CD4, CD8, CD25) and NK-cell subsets (CD16, CD56), which will be determined via multiparameter FACS analysis (percentage and absolute numbers) in peripheral blood at Dr. James Reuben's laboratory of MD Anderson.
    - Serum analysis of herpes simplex virus (HSV) type 1 serology with immunoglobulin (Ig)G and IgM (ELISA)
- To assess distant tumor tissue changes by evaluating necrosis and immune cell infiltration (T-/B-/NK-Cell, macrophage, dendritic cell) by immunohistochemistry assay (CD3, CD4, CD8, CD20, CD16, CD56, Granzyme B, cleaved caspase 3, and Ki-67) when distant tumor sample is obtained. If the sample volume is ample, additional immunohistochemistry assays will be performed for CD45RO, TIA-1, FoxP3, CD25, OX-

40, CD57, CD1a, CD208, myeloperoxidase, CD68, COX-2, MHC Class I and MHC Class II in Dr. Savitri Krishnamurthy's laboratory at MD Anderson.

Figure 1:Systemic immune response expected to be related to talimogene laherparepvec administration



Talimogene laherparepvec induces systemic immune reaction through activation of dendritic cell, and enhance cellular immunity (IL-2, IL-12, TNF-a, IFN-a, CD3, CD4, CD8, CD25,CD45RO, TIA-2, FoxP3, OX40, CD1a). Cytotoxic T-lymphocyte (CTL) is estimated to offense distant cancer cells by apoptosis mechanism (cleaved caspase3) and humoral immunity was not determined to involved this systemic immunity. However, the activation of dendritic cells (CD208, MHC class I and II) may subsequently activate NK-cells (CD16, CD56, Granzyme B, CD57) and B-cells (CD20). Other leukocyte such as neutrophil (myeloperoxidase) and monocyte (CD68) are currently undetermined their function within systemic immune reaction induced by talimogene laherparepvec.

2.0 Background

2.1 Overview of breast cancer local recurrence

2.1.1 Breast cancer local recurrence

Recurrent breast cancer is commonly incurable, and multimodality treatment options have been developed. Following mastectomy or breast-conserving surgery, the 10-year incidence of locoregional recurrence (LRR) is about 13%[1]. The local recurrence rate of inflammatory breast cancer (IBC) is higher than that of locally advanced non–inflammatory breast cancer [2]. In particular, breast cancer patients with LRR have been found to have 5-year disease-free survival (DFS) rates of 13%-37% and OS rates of 21%-50%[3-5]. Moreover, the outcome is poorer after LRR than after local disease only[6], and concomittant distant metastases carry an even more dismal outcome. In this protocol, we propose a new treatment modality to increase the control rate of measurable and non-measurable disease and to prolong outcomes.

2.1.2 Current management for local recurrence

Many breast cancer patients would have mastectomy and others would have conservative surgery. However, IBC is generally treated with mastectomy when diagnosed, some locally advanced non-IBC patients with local recurrence who previously underwent breast-conserving surgery might have undergo mastectomy for local recurrence[7], although many patients with local recurrence would prefer to receive chemotherapy and/or radiation therapy as a salvage treatment because of their inoperable status. Some studies have reported LRR rates following neoadjuvant chemotherapy and breast-conserving surgery to be as high as 26%. More recent reports document rates of 7%-16%, largely equivalent to those seen in patients undergoing initial mastectomy[8-14]. Furthermore, systemic therapy for local recurrence may be preferred for marginally surgical candidates since minor residual disease before radiation therapy is a better prognostic indicator in this population[15], although NCCN guideline defined systemic treatment would be secondary to local treatment. In addition, breast cancer patients with local recurrence frequently have distant metastases, and these patients are candidates for systemic treatment.

2.1.3 Evaluation of treatment effects on locally recurrent breast cancer

A proportion of patients with locally recurrent breast cancer have non-measurable disease. As long as we accrue only patients with locally recurrent breast cancer, we will include those who have only non-measurable local lesions. Defining the overall response rate in this population would be difficult; however, it is reasonable to define the rate of control for measurable and immeasurable disease with PFS and OS. In addition, some biological agents such as imatinib have cytostatic effects on gastrointestinal stromal tumor but lack tumor shrinkage properties; that is, although the size of tumors are similar, the agents induce tumor necrosis. The proposed study agent is expected to induce tumor necrosis and yield overall response rate and disease control rate that is a reasonable surrogate for its efficacy.

2.2 Potential anti-breast cancer drug for targeting local disease

Patients with locally recurrent breast disease frequently undergo multimodal treatment at the first occurrence of breast cancer, and because local treatment modalities such as surgical intervention and radiation are difficult to add, they subsequently receive systemic therapy. Talimogene laherparepvec (JS1/ICP34.5-/ICP47-/GM-CSF; OncoVEX^{GM-CSF}) was developed to eliminate solid tumors and has since been considered as a potential treatment option for body surface tumors. In addition to talimogene laherparepvec injected area, this agent would modify immune response and could work on distant metastases. Hence, locally recurrent breast disease matches as target disease for talimogene laherparepvec regardless of concomitant distant metastases, hence talimogene laherparepvec is possible new local treatment option.

3.0 Rationale

Local recurrence of breast cancer can result in substantial morbidity and also frequently leads to systemic metastases. Modalities used to treat locally recurrent breast cancer include chemotherapy, hormone therapy, radiation therapy, and surgery. Compared with distant metastases, local recurrence is staged as possible curative status if additional surgery is available, however this opportunity is limited for patients with minor local disease having had conservative

surgery. In addition, survival improvement has not well been demonstrated due to lack of new modality of local treatment.

Current treatment modalities for locally recurrent breast cancer depend on the operability of lesions, disease aggressiveness, previous chemotherapy or radiation therapy, and histologic subtypes; thus, a new modality for treating local disease is needed, since systemic therapy is currently the last resort intervention. Talimogene laherparepvec is immunotherapy with a dual mechanism of generating local tumor lysis and systemic antitumor immune response. In a previous phase I study, talimogene laherparepvec as a single agent was shown to induce tumor necrosis in breast cancer.

The purpose of this study is to determine the local and systemic antitumor efficacy of talimogene laherparepvec in locally recurrent breast cancer patients with or without distant metastases, as evidenced by improved overall response rates. This will be the first study to use biopsy of distant disease to demonstrate whether systemic immune modulation has antitumor efficacy in breast cancer patients. We will also evaluate the antitumor effects of talimogene laherparepvec via comprehensive imaging such as chest x-ray, ultrasound, computed tomography (CT), and positron emission tomography ^{16}/CT as clinically indicated. In addition, we will conduct multiple biological correlative studies to understand the role of immune response activated by talimogene laherparepvec in breast cancer. Patients with initially inoperable local recurrence can be candidates for surgery with curative intent if their tumors become operable.

4.0 Product drug information

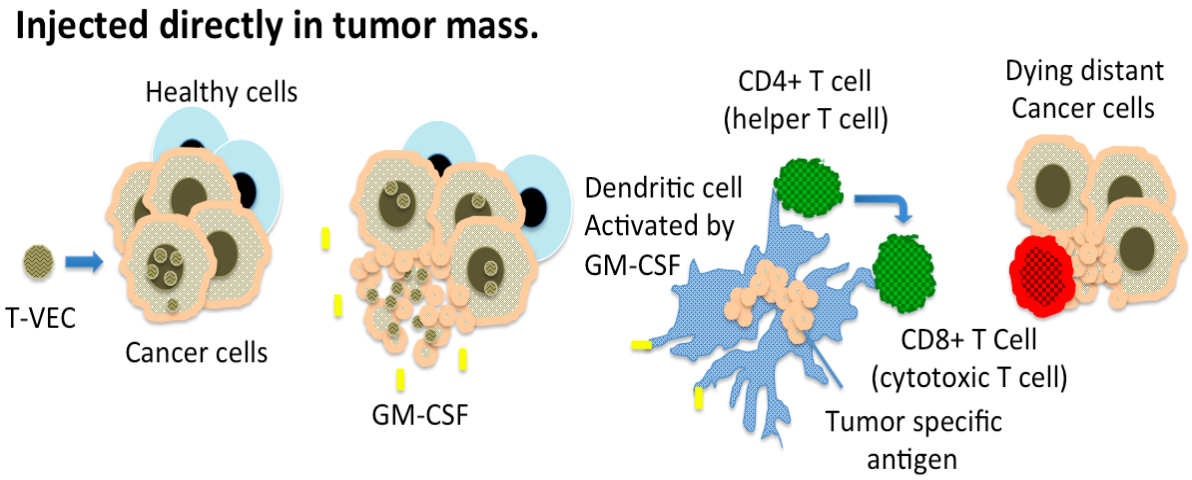
4.1 Mechanism of action of talimogene laherparepvec

Talimogene laherparepvec, which is a genetically modified HSV type 1 (HSV1), has dual mechanisms for eliminating solid tumors (Figure 2). First, HSV1 in which the neurovirulence factor ICP34.5 is inactivated has the potential to cause tumor lysis in several tumor models. Second, ICP47 deletion via the up-regulation of US11, which occurs following this mutation, functions to block antigen processing in HSV-infected cells, so the immune stimulating properties of the virus are expected[17]. In addition, US11 gene expression enhances tumor-selective viral replication[18], and GM-CSF is a potent immune stimulator and enhances immune response[17] by activating dendritic cell and promoting antigen presentation to CD4+ or CD8+ T cells. Activated CD8+ cytotoxic T cells are expected to offense distant tumor cells. The infected neoplastic cells are killed via replicating virions, and release them. As viruses kill neoplastic cells, cross-resistance with other treatment modalities, such as chemotherapy, hormonal therapy, and radiation therapy, does not arise. Thus, immunotherapy could complement current standard treatment options.

Oncolytic replication-competent HSV can infect and kill tumor cells, but normal cells are not terminated by the cytopathic effects of HSV, as shown in an in vitro investigation of the efficacy and toxicity of oncolytic HSV in breast cancer[19]. A phase 1 study of talimogene laherparepvec (14 cases of breast cancer out of 30 total cases)[18], revealed no major responses in any cases, including melanoma; however, four patients with breast cancer had local disease stabilization. In the phase 1 study, talimogene Laherparepvec was shown to be effective up to 6 cm from the

injection site. Considering side effects and viral replication, the investigators concluded that talimogene laherparepvec injections every 2-3 weeks were appropriate for future clinical trials.

Figure 2: Mechanism of talimogene laherparepvec against local and distant tumor[20]



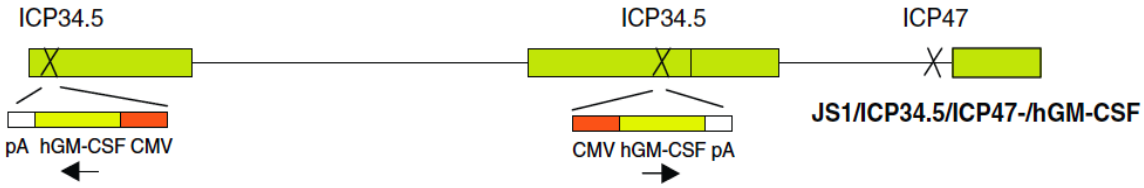
Talimogene laherparepvec (OncoVEX^{GM-CSF}) is attenuated herpes simplex virus type 1 (HSV) and modified to replicate only in tumor cells. This has two separate treatment strategies and the first is oncolytic potential due to amplified HSV in tumor cells. After the tumorlysis occurred, talimogene laherparepvec activate dendritic cells with GM-CSF effect, and antigen would be presented through dendritic cell to CD4+ and CD8+ T cells. Activated CD8+ cytotoxic T-cell induces systemic immunity for breast cancer located at distant organ as second option.

4.2. Description of talimogene laherparepvec

The preparation and testing of the cell banks, viral seed stock, and talimogene laherparepvec clinical material were conducted in accordance with current Good Manufacturing Practices (cGMP), relevant the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [21] guidelines, European Directives, and the U.S. Pharmacopeia and Title 21 Code of U.S. federal regulations. In particular, the European Pharmacopoeia (Ph Eur) monograph on viral vaccine testing, ICH considerations on oncolytic viruses, and U.S. Food and Drug Administration (FDA) Points to Consider – Characterization of Cell Lines Used to Produce Biologicals (1993) have been followed for the safety testing of talimogene laherparepvec.

Talimogene laherparepvec has been extensively characterized using growth curves, buoyant density gradients, restriction mapping, size exclusion chromatography, epitope mapping, Western blotting, and electron microscopy. Additionally, the talimogene laherparepvec genome has been sequenced (Figure 3). Talimogene laherparepvec has been formulated in phosphate buffered saline (PBS) and a sugar stabilizer for direct intratumoral injection. The talimogene laherparepvec formulation is summarized in Table 1.

Figure 3: Schematic diagram of Talimogene laherparepvec



The sequenced result of talimogene laherparepvec

Table 1: Talimogene laherparepvec formulation

Talimogene laherparepvec is intended for direct injection into suitable non-neurological solid tumors. Dose schedules may vary for different tumors and indications. The initial dose should usually be lower than subsequent doses.

Name of ingredients	Quantity per mL	Function	Reference to standards
Active substance: talimogene laherparepvec	1 x 10^6 PFU or 1 x 10^8 PFU	Active	In-House Standard
Excipients: Phosphate buffered saline (PBS) pH 7.2	To 1.0 mL	Buffer	USP
sorbitol	20 mg	stabilizer	USP
myo-inositol	40 mg	stabilizer	USP

4.3. Drug supply and storage

Talimogene laherparepvec is provided as a sterile frozen liquid in a single-use 2.0 mL cyclic olefin polymer plastic resin vial . Each vial contains talimogene laherparepvec at a nominal concentration of 10^6 plaque forming unit (PFU)/mL or 10^8 PFU/mL in solution for intratumoral injection. Talimogene laherparepvec doses (1 mL extractable volume) will be applied. Vials will be sealed with elastomeric stoppers (with a fluoropolymer laminated plug and a crosslinked silicon top), and an aluminum seal with a flip-off dust cover. The vial caps are color coded to easily distinguish between the 10^6 PFU/mL (light green) and 10^8 PFU/mL (royal blue) vial concentrations.

Talimogene laherparepvec should be stored away from light and according to the storage and expiration information provided on the label that is affixed to the package containing the investigational product.

Talimogene laherparepvec should be thawed per the instructions provided in the Appendices section 15.7 and/or the package insert in Appendix P in PDOL. Vials should be checked for cracks or damage that may occur during the thawing process if not performed properly. Damaged

product should not be administered and after confirmation from Amgen, damaged vials should be destroyed on site.

4.4. Effects of talimogene laherparepvec in human

4.4.1. Talimogene laherparepvec clinical study

Fifteen clinical studies have been or are being conducted with at least 1 subject enrolled as of 30 June 2015. Seven studies are complete, 7 studies are ongoing, and 1 was terminated early. Among the ongoing studies is the non-interventional registry study to investigate the long-term survival and safety of subjects previously treated with talimogene laherparepvec in any study. In addition to these 15 studies, two expanded access protocols, one each in the US and EU, are also ongoing.

Table 2: Summary of clinical studies

Study Number	Study Title	Study Status	Dose, Duration	Number of Subjects
Various Tumor Types				
001/01	First Administration to Man of an Oncolytic Herpesvirus-1 Vector Containing A Transgene For Granulocyte Macrophage Colony Stimulating Factor (OncoVEX^{GM-CSF}): A Study of its Safety, Biodistribution and Biological Activity	Complete	Part 1: 10^6, 10^7, 10^8 PFU/mL Single dose, dose-escalation study Part 2: A: 10^6, 10^7 or 10^8, 10^7 or 10^8 PFU/mL (Seronegative subjects) B: 10^6, 10^8, 10^8 PFU/mL or 10^8, 10^8, 10^8 PFU/mL (Seropositive subjects) Up to 3 doses; For seronegative subjects, the 2nd and 3rd doses were administered only after HSV-1 seroconversion evidence	Part 1: 13 Part 2: 17
Melanoma				
002/03	A Phase 2 Study of the Efficacy, Safety, and Immunogenicity of OncoVEX^{GM-CSF} in Patients with Stage IIIc and Stage IV Malignant Melanoma	Complete	10^6, 10^8 PFU/mL 8 doses over 15 weeks; if biological activity was observed, an additional 16 doses could have been administered	50
002/03-E	An Extension Protocol for the Extended Use of OncoVEX^{GM-CSF} for Eligible Patients Participating in Study 002-03: A Phase 2 Study of the Efficacy, Safety and Immunogenicity of OncoVEX^{GM-CSF} in Patients with Stage IIIc and Stage IV Malignant Melanoma	Complete	10^8 PFU/mL Every 2 weeks until discontinuation criteria were met	3

Study Number	Study Title	Study Status	Dose, Duration	Number of Subjects
Melanoma				
005/05[a]	A Randomized Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of Treatment with OncoVEX^{GM-CSF} Compared to Subcutaneously Administered GM-CSF in Melanoma Patients with Unresectable Stage IIIb, IIIc and IV Disease	Complete	10^6 PFU/mL followed by 10^8 PFU/mL Every 2 weeks until protocol-specified criteria were met	436 enrolled[b]: 295 talimogene laherparepvec 141 GM-CSF
005/05-E	An Extension Protocol to Evaluate the Efficacy and Safety of Extended Use Treatment with OncoVEX^{GM-CSF} for Eligible Melanoma Patients Participating in Study 005/05	Complete	10^6 PFU/mL followed by 10^8 PFU/mL Every 2 weeks until protocol-specified criteria were met	31 enrolled: 28 talimogene laherparepvec 3 GM-CSF
20110264[c]	A Phase 1b/2, Multicenter, Open-label Trial to Evaluate the Safety and Efficacy of Talimogene Laherparepvec and Ipilimumab Compared to Ipilimumab Alone in Subjects With Previously Untreated, Unresectable, Stage IIIb-IV Melanoma	Ongoing. Phase 1 fully enrolled, Phase 2 Open	10^6 PFU/mL followed by 10^8 PFU/mL every 2 weeks until protocol-specified criteria were met, with the addition of ipilimumab 3mg/kg every 3 weeks x 4 doses starting at week 6	Phase 1b: 19 enrolled. Phase 2: 200 (planned)

Study Number	Study Title	Study Status	Dose, Duration	Number of Subjects
Melanoma				
20110265	A Phase 1b/3, Multicenter, Open-label Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresected, Stage IIIB to IVM1c Melanoma (MASTERKEY-265)	Ongoing	Phase 1b: . 10^6 PFU/mL followed by 10^8 PFU/mL 21 days later. Subsequent doses of 10^8 PFU/mL are administered every 2 weeks. Pembrolizumab: 200 mg -every 2 weeks. Phase 3: 10^6 PFU/mL followed by 10^8 PFU/mL 21 days later. Subsequent doses of 10^8 PFU/mL are administered every 2 weeks until week 9 and every 3 weeks thereafter. Pembrolizumab: 200 mg every 3 weeks	Phase 1b:21 enrolled Phase 3: 660 (planned)

Study Number	Study Title	Study Status	Dose, Duration	Number of Subjects
Melanoma				
20110266	A Phase 2, Multicenter, Randomized, Open-label Trial Assessing the Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Resectable, Stage IIIB to IVM1a Melanoma	Ongoing	Arm 1: 10^6 PFU/mL followed by 10^8 PFU/mL 28 days later. Subsequent doses of 10^8 PFU/mL are administered every 2 weeks until protocol-specified criteria are met. Surgery follows. Arm 2: Surgery alone.	75 per arm (planned)
20120139	A Registry Study to Evaluate the Survival and Long-Term Safety of Subjects with Melanoma Who Previously Received Talimogene Laherparepvec	Ongoing	Not Applicable	Not applicable
20120166	A Phase 3b, Multicenter, Open-label, Single-arm, Expanded Access Protocol of Talimogene Laherparepvec for the Treatment of Subjects With Unresected, Stage IIIB to IVM1c Melanoma	Ongoing	10^6 PFU/mL followed by 10^8 PFU/mL 21 days later Subsequent doses administered every 2 weeks until protocol-specified criteria were met	100 (planned)

Study Number	Study Title	Study Status	Dose, Duration	Number of Subjects
Melanoma				
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	Ongoing	10^6 PFU/mL followed by 10^8 PFU/mL Second dose administered 21 days after the initial dose, subsequent doses administered every 2 weeks until protocol-specified criteria were met	50 to 60 (planned)
20120325	A Phase 2, Multicenter, Open-label, Single-arm Trial to Evaluate the Correlation Between Objective Response Rate and Baseline Intratumoral CD8+ Cell Density in Subjects With Unresected Stage IIIB to IVM1c Melanoma Treated with Talimogene Laherparepvec	Ongoing	10^6 PFU/mL followed by 10^8 PFU/mL 21 days later. Subsequent doses administered every 2 weeks until protocol-specified criteria were met	110 (planned)

Study Number	Study Title	Study Status	Dose, Duration	Number of Subjects
Pancreatic Cancer				
005/04	Targeted Delivery of OncoVEX^{GM-CSF} by Endoscopic Ultrasound (EUS)-Guided Fine Needle Injection (FNI) in Patients with Irresectable Pancreatic Cancer: A Pilot Multinational Experiment on Safety and Proof of Concept	Complete	4 cohorts each received 3 doses, each 3 weeks apart: 1) 10^4, 10^5, 10^5 PFU/mL 2) 10^5, 10^6, 10^6 PFU/mL 3) 10^6, 10^7, 10^7 PFU/mL 4) 10^6, 10^8, 10^8 PFU/mL	17
Head and Neck Cancer				
004/04	An Exploratory Study Of The Safety And Biological Activity Of OncoVEX^{GM-CSF} In Combination With Radiotherapy And Cisplatin In The Treatment Of Locally Advanced Epithelial Cancer Of The Head And Neck	Complete	4 cohorts each received 4 injections once every 3 weeks: 1) 10^6, 10^6, 10^6 , 10^6 PFU/mL 2) 10^6, 10^7, 10^7, 10^7 PFU/mL 3) 10^6, 10^8, 10^8, 10^8 PFU/mL 4) 10^6, 3 additional doses up to 10^8 PFU/mL	17
006/09	A Phase 3 Randomized Trial of Concurrent Cisplatin and Radiotherapy with or without OncoVEX^{GM-CSF} in Previously Untreated Patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck	Study terminated	10^6 PFU/mL followed by 10^8 PFU/mL	528 (planned) 5 enrolled: 2 talimogene laherparepvec 3 standard of care

DRR = durable response rate, GM-CSF = granulocyte macrophage colony stimulating factor, HSV = herpes simplex virus, OS = overall survival, PFU = plaque-forming units.
[a] Data cutoff for primary analysis for DRR is 21 December 2012; data cutoff for primary analysis for OS is 31 March 2014.
[b] 439 randomizations occurred, but one subject was later determined to have been randomized 3 times (at 3 different sites) and was therefore excluded from the ITT set.
[c] Data cutoff for 20110264 (Phase 1b portion) is 05 May 2014.

*NCT numbers: 005/04: NCT00402025; 005/05: NCT00769704; 006/09: NCT01161498

4.4.2. Pharmacodynamics and pharmacokinetics in humans

In previous clinical studies of talimogene laherparepvec, samples were taken at protocol-specified times before and after talimogene laherparepvec was administered to assess viral shedding, biodistribution, and the sero-status of patients with regard to HSV. Occasionally, investigational swabs and tissue samples (biopsies) were analyzed for the presence of talimogene laherparepvec at the request of the investigator.

4.4.3. Safety and efficacy of talimogene laherparepvec in phase 1 study of solid tumor

Study 001-01 was a phase 1, open-label study to evaluate the safety, biodistribution, and biological activity of 3 dose levels of talimogene laherparepvec in patients with advanced solid tumors with metastases in the skin or subcutaneous tissue. In part 1 of the study, a single dose of talimogene laherparepvec was administered to cohorts of 4 patients. The first dose group received talimogene laherparepvec at a dose of 10^6 PFU/mL, the second dose group received 10^7 PFU/mL, and the third dose group received 10^8 PFU/mL. In part 2 of the study, the patients received up to 3 doses administered every 14 days at the following 3 dose levels: group A received 10^6, 10^7, and10^7 PFU/mL; group B received 10^8, 10^8, and 10^8 PFU/mL; and group C received 10^6, 10^8, and 10^8 PFU/mL. The investigational product was administered directly into a cutaneous or subcutaneous tumor.

Thirty patients participated in the study. Of those, 14 had adenocarcinoma of the breast, 9 had malignant melanoma, 4 had squamous cell carcinoma of the head and neck, and 3 had various other solid tumors. A total of 8 patients withdrew from the study prematurely: 3 (10%) withdrew

owing to progressive disease, 2 (6%) withdrew owing to serious adverse events, 1 (3%) withdrew consent, and 2 (6%) withdrew for other reasons.

Almost all the patients (29 of 30; 97%) experienced at least 1 adverse event during the study. Most of the adverse events reported were mild or moderate in severity. The most commonly reported adverse events across all treatment groups were pyrexia (19 patients; 63%), neoplasm progression (9patients; 30%), rigors (8 patients; 27%), post-procedural complications (8 patients; 27%), nausea (7patients; 23%), anorexia (7 patients; 23%), vomiting (6 patients; 20%), and injection site reaction (6 patients; 20%).

Of 30 patients, 16 (53%) had serious adverse events. The most frequently reported serious adverse events were neoplasm progression (13%), post-procedural complications (13%), pyrexia (13%), dyspnea (10%), and injection site reaction (7%). All other serious adverse events were reported in one patient each. Two patients withdrew from the study prematurely owing to serious adverse events, and 5 deaths were reported; of those deaths, 3 were attributed to disease progression, 1 to aspiration pneumonia, and 1 to an accidental overdose of analgesia.

There was no meaningful difference in the overall incidence of adverse events following the first and second injections, with 27 of 30 patients (90%) reporting adverse events after the first injection and 13 of 15 patients (87%) reporting adverse events after the second injection. There was, however, a reduction following the third injection, with 11 of 15 patients (73%) reporting adverse events.

In the first 2 single-dose groups (10^6 and 10^7 PFU/mL), the 4 patients (3 receiving 10^7 PFU/mL and 1 receiving 10^6 PFU/mL) who were seronegative to HSV-1 at study entry all developed flu-like symptoms such as fatigue, rigors, and pyrexia as well as erythema around the injected lesion. Two seronegative patients who received talimogene laherparepvec at 10^7 PFU/mL developed an erythematous rash with scattered vesicles in the skin. Shedding of the virus from some of the injected nodules also occurred; however, the virus was not detected on the outer dressing of the injection site. The events were transient and self-limiting, and no sequelae were noted. It was therefore concluded that seronegative patients should receive a lower initial dose (i.e., 10^6 PFU/mL) of talimogene laherparepvec.

In analyses to detect virus via specific quantitative PCR in blood, results were positive at one or more time points for 10 of 30 patients. Urine was positive for virus at one or more time points for 2 patients. Generally, in the repeated-dose part of the study, virus was noted only within 8 hours after the injection.

Four patients experienced shedding of live virus from the injection site, although in all cases, this was contained within the occlusive dressing, and no virus was detected on swabs of the outside of the dressing. Three of these patients were seronegative at baseline; 2 of the patients were given a first dose of talimogene laherparepvec at 10^7 PFU/mL, 1 received 10^8 PFU/mL, and 1 received 10^6 PFU/mL. Three patients had transient cutaneous vesicles or vesicle-like areas at various sites including the mouth, nose, forehead, cheek, right buttock, back, and sternum during weeks 2 and 3 of the study. Two of these patients were seronegative for HSV1 at enrollment and given a single dose of talimogene laherparepvec at 10^7 PFU/mL. The third patient who had vesicle-like areas was also seronegative at enrollment and was given 3 doses of talimogene

laherparepvec (10^6 PFU/mL, 10^7 PFU/mL, and 10^7 PFU/mL). Swabs were taken from these sites, but no virus was detected. In subsequent studies, a first dose of 10^6 PFU/mL has been administered, followed by higher doses of 10^8 PFU/mL, after this higher dose shedding is seen only rarely. Swabs were also taken from sites other than the injected nodule for 4 additional patients, and virus was not detected in any of these patients.

The secondary objective of the study was to identify signs of biological activity of the virus in the treated patients. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1).

Eight patients (27%) had stable disease, 19 patients (63%) had progressive disease, and 3 (10%) were not evaluable. In addition to tumor assessments, the study also defined a response if tumor necrosis was seen in a biopsy. Nineteen patients had biopsies containing tumor tissue. Of these, 13 biopsies (68%) showed evidence of partial or extensive tumor necrosis. One additional tumor-containing biopsy showed apoptosis. Thus, 14 of 19 patients (74%) with biopsies containing tumor tissue had necrosis or apoptosis.

HSV was detected by the use of a polyclonal antibody to stain biopsies taken from talimogene laherparepvec–injected tumors. Virus was shown to co-locate with areas of necrosis in the tumor; all biopsies with necrosis stained strongly for HSV. Non-necrotic and non-tumor tissues in the biopsies very rarely stained for HSV.

Tumor biopsies were stained for a variety of T cells (expressing CD3, CD4, CD8, CD30, and CD68 markers). All biopsies were positive for these cells. However, no obvious patterns emerged and, in the absence of baseline data, it is not possible to conclude that T cell levels were elevated as a result of treatment.

Quantitative PCR also was performed to evaluate the presence of hGM-CSF mRNA in order to measure talimogene laherparepvec –encoded GM-CSF versus endogenous GM-CSF. Of 13 biopsies with partial or extensive tumor necrosis, 11 (84.6%) showed measurable quantities of talimogene laherparepvec encoded GM-CSF mRNA, and the level of mRNA expressed was dose dependent (i.e., more GM-CSF mRNA was expressed after administration of higher doses of talimogene laherparepvec). Additionally, seronegative patients expressed more GM-CSF mRNA than did seropositive patients.

4.5. Registration and marketing experience

Talimogene laherparepvec has received regulatory approval for marketing in US and Europe.

US:

Talimogene laherparepvec is approved in melanoma. Intralesional injection of talimogene laherparepvec, also known as IMLYGIC®, has been approved by the United States Food and Drug Administration (FDA) for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in adult patients with melanoma recurrent after initial surgery. However, it has not been shown to increase OS or have an effect on metastases to internal organs including the liver and lungs.

Europe:

IMLYGIC® is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease the first oncolytic viral therapy. It is proposed that IMLYGIC®, be initiated and supervised by a qualified physician experienced in the treatment of cancer.

4.6. Important Identified and Potential Risks, Adverse Drug Reaction (ADRs)

Consult the current Investigator's Brochure (IB) for the full information on Identified and Potential Risks of talimogene laherparepvec and Adverse Drug Reaction (ADRs).

5.0. Patient eligibility

Up to 36 patients will be enrolled in the study. Patients must to meet the following criteria to be eligible for the study.

5.1. Inclusion criteria

5.1.1. Histologic confirmation of breast carcinoma.

5.1.2. Histologic confirmation of recurrence of chest wall / cutaneous, subcutaneous or nodal tumors disease with or without distant metastasis.

5.1.3 Patients must have failed at least 1 systemic regimen or have clinical stable disease with capecitabine, hormonal therapy (with or without mTOR inhibitor or CDK4/6 inhibitor), or anti HER-2 therapy (trastuzumab, pertuzumab, ado-trastuzumab emtansine, lapatinib) for at least 2 months after their diagnosis of locoregional/metastatic disease.

5.1.4. Concurrent radiation therapy is permitted after the study treatment is initiated so long as the planned radiation field doesn't overlap with planned injection sites.

5.1.5. Age 18 years or older.

5.1.6. Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1

5.1.7. Adequate hematologic function

- Absolute neutrophil count $\geqq 1.0 \times 10^9$/L. If patient is taking CDK4/6 inhibitor or capecitabine, there is a need for maintaining ANC ≥ 1.0 consistently for at least 2 months without dose changes.
- Platelet count $\geqq 75 \times 10^9$/L. If patient is taking CDK4/6 inhibitor, ado-trastuzumab emtansine or capecitabine, there is a need for maintaining platelet count $\geq 75 \times 10^9$/L without dose changes.
- Hemoglobin $\geqq 8.0$ g/L
- International normalization ratio (INR) or prothrombin time (PT)/ partial thromboplastin time (PTT)/ activated PTT (aPTT) $\leqq 1.5$ x ULN, unless the subject is receiving anticoagulant therapy, in which case PT and PTT/aPTT must be within therapeutic range of intended use of anticoagulants

5.1.8. Adequate renal function

- Serum creatinine ≤ 1.5 x upper limit of normal (ULN), OR 24-hour creatinine clearance ≥ 60 mL/min for subject with creatinine levels > 1.5 x ULN. (Note: Creatinine clearance need not be determined if the baseline serum creatinine is ≦ 1.5 x ULN. Creatinine clearance should be determined per institutional standard).

5.1.9. Adequate hepatic function

- Aspartate aminotransferase (AST) ≦ 2.5 x upper limit of normal (ULN) if liver metastases present
- Alanine aminotransferase (ALT) ≦ 2.5 x ULN if liver metastases present
- Total bilirubin ≦ 1.5 x ULN, OR direct bilirubin ≤ ULN for a subject with total bilirubin level > 1.5 x ULN

5.1.10 Subjects must be candidate for intralesional injection into cutaneous, subcutaneous or nodal tumors with or without image ultrasound guidance defined as one or more of the following At least 1 injectable lesion ≥5 mm in longest diameter, multiple injectable lesions that in aggregate have a longest diameter of ≥ 5 mm.

5.1.11. Female patients of childbearing potential must have a negative urine or serum pregnancy test no more than 3 days prior to starting study drug.

5.1.12. Patients must be able and willing to give written informed consent.

5.2 Exclusion criteria

5.2.1. Patients who have operable disease with curable intent, and/or are candidates for radiation therapy for local control.

5.2.2. Patients receiving concurrent anti-cancer therapy (chemotherapy except Capecitabine or ado-trastuzumab emtansine , immunotherapy) while taking the study medication, or have previously received talimogene laherparepvec or any other oncolytic virus.

5.2.3. Patients with metastatic sites that necessitate chemotherapy (except Capecitabine or ado-trastuzumab emtansine) .

5.2.4. Known active central nervous metastases. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids >10 mg/day of prednisone or equivalent. The exception does not include carcinomatosus meningitis which is excluded regardless of clinical stability.

5.2.5. More than three lesions per organ for visceral metastases except for lung or lymph node.

5.2.6. History or evidence of active autoimmune disease that has required systemic treatment (i.e., use of corticosteroids, immunosuppressive drugs or disease modifying agents)

Replacement therapy (eg, thyroxine for hypothyroidism, insulin for diabetes or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment for autoimmune disease.

5.2.7. A concurrent disease or condition that would render the patient inappropriate for study participation or any serious medical disorder that would interfere with the patient's safety.

5.2.8. History of other malignancy within the past 5 years with the following exceptions:

- Adequately treated non melanoma skin cancer without evidence of disease at the time of enrollment
- Adequately treated cervical carcinoma in situ without evidence of disease at the time of enrollment
- Adequately treated breast ductal carcinoma in situ without evidence of disease at the time of enrollment
- Prostatic intraepithelial neoplasia without evidence of prostate cancer at the time of enrollment.

5.2.9. Active infection that necessitates intravenous or oral antibiotics.

5.2.10. Evidence of immune suppression as following:

- Known human immunodeficiency virus (HIV) infection or AIDS
- Known leukemia or lymphoma
- Primary immunodeficiency state such as Severe Combined Immunodeficiency Disease.
- Concurrent opportunistic infection.
- Receiving systemic immunosuppressive therapy (> 2 weeks) including oral steroid doses > 10 mg/day of prednisone or equivalent within 7 days prior to the initiation of study treatment.
- Known hepatitis B or C infection
- Congenital or acquired cellular and/or humoral immune deficiency.
- Other signs or symptoms of immune system suppression

5.2.11. Active herpetic skin lesions or prior complication of HSV-1 infections (e.g. herpetic encephalitis or keratitis).

5.2.12. Currently pregnant or breast-feeding, or planning to become pregnant during study treatment and through 3 months after the last dose of study treatment.

5.2.13 Female subject of childbearing potential who is unwilling to use acceptable method(s) of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec. (Women of not childbearing potential: post-menopausal [age > 55 years with cessation of menses > 12 months or < 55 years but not spontaneous menses for at least 2 years or < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), and with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal

range" for the laboratory involved] or who have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

5.2.14 Sexually active subjects and their partners unwilling to use male or female latex condom to avoid potential viral transmission during sexual contact while on treatment and within 3 months after treatment with talimogene laherparepvec.

5.2.15. Currently enrolled in another clinical trial for investigational drugs, procedures or device (excluding non-cancer treatment trials) or receipt of an investigational agent or device within 4 weeks of the initiation of study treatment

5.2.16. Intermittent or chronic treatment with antiherpetic drugs, except for topical agents.

5.2.17. Patients who is known sensitive to any of the products or components to be administered during treatment with talimogene laherparepvec.

5.2.18. Chronic oral or systemic steroid medication use at a dose of >10 mg/d of prednisone or equivalent [steroids with low systemic absorption (e.g. triamcinolone hexacetonide) injected into joint space are allowed]

5.2.19. Prior therapy with tumor vaccine, or received live vaccine within 28 days prior to the initiation of study treatment.

5.2.20 Subjects who are unwilling to minimize exposure with his/her blood or other body fluids to individuals who are at higher risks for HSV-1 induced complications such as immunosuppressed individuals, individuals known to have HIV infection, pregnant women, or infants under the age of 3 months, during talimogene laherparepvec treatment and through 30 days after the last dose of talimogene laherparepvec.

5.2.21 Prior immunosuppressive, chemotherapy, radiotherapy (in which the field encompassed a planned injection site), biological cancer therapy (monoclonal antibodies), or major surgery within 28 days prior to enrollment or has not recovered to CTCAE grade 1 or better from adverse event due to cancer therapy administered more than 28 days prior to enrollment.

5.2.22 Prior radiotherapy in which the field does not overlap the injection sites or non-immunosuppressive targeted therapy within 14 days prior to enrollment or has not recovered to CTCAE grade 1 or better from adverse event due to cancer therapy administered more than 14 days prior to enrollment

5.2.23 Patients who have extensive skin disease, defined as total area of skin involvement/ lesions that comprise ≥10% of body surface area. Refer to “Rule of Nines” in Appendix 15.6 that will be the guide for specific percentages per body part(s). Skin involvement comprising ≥5% to upper anterior chest wall or ≥5% to upper posterior back is excluded.

6.0. Treatment plan

6.1 Talimogene laherparepvec injection

Talimogene laherparepvec will be given via intra-tumoral injection at visible locally recurrent breast cancer site and skin metastases if indicated at an initial dose of 10^6 PFU/mL for all sample size of 35. If patient has multiple lesions the lesion selection as the following:

1) If the largest lesion is > 5cm, only this lesion will be used for injection;
2) If the largest lesion is < 5.0 cm, we will prioritize the size of the lesions (from large to small), and administer talimogene laherparepvec based on injection guideline in Table 3 below. The maximum dose of each course should not exceed 4.0 mL.
3) If patients do not have distant metastases, the lesion of lowest priority for injection should be left uninjected at least until it is biopsied.

The injection dose will not be affected by patients' actual body weight. The second talimogene laherparepvec dose will be administered 10^8 PFU/mL on day 22, and talimogene laherparepvec will be administered every 2 weeks after the second course with same dose with the maximum dose of 4.0 mL for each course (Figure 4). The injection dose varies according to the tumor spread area and using the talimogene laherparepvec injection volume guideline based on tumor size (Table 3). Distribution of the injection to separate sites will be permitted if the lesion is more than 5.0 cm diameter and/or multiple lesions. When disease diameter is greater than 5.0 cm and difficult to inject uniformly, we divide disease location tetrameric injection site with 1.0 mL administration each. On each treatment day, injections should be prioritized as follows:

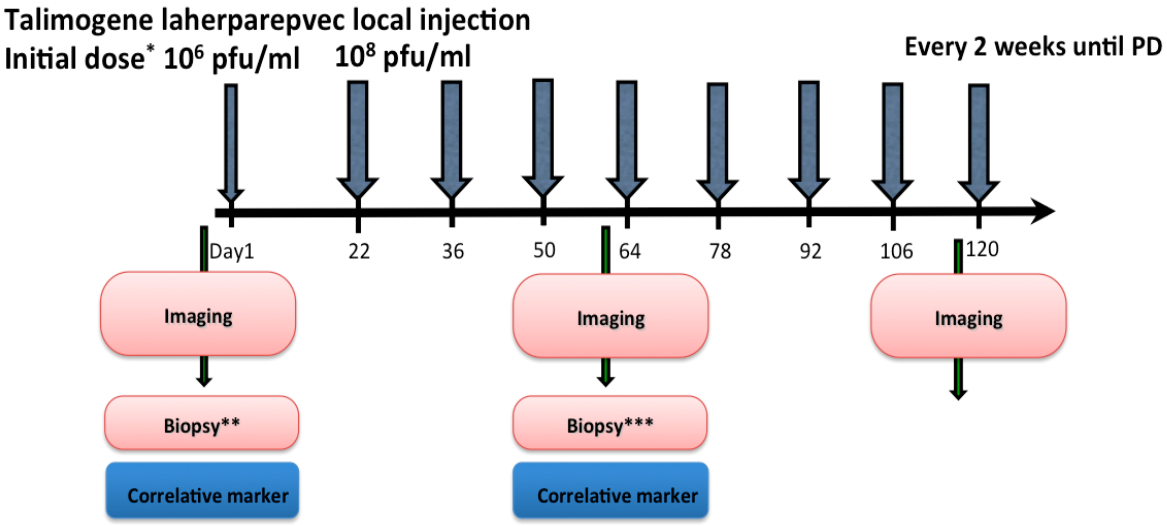
- any new injectable tumor that has appeared since the previous injection
- by tumor size, beginning with the largest tumor and then the second largest tumor if agent available, otherwise treat in the following courses
- by tumor size, when similar size tumor exist, prioritize one and then the other tumor if agent available, otherwise treat in the following courses
- by tumor size, when huge tumor exist (greater than 10.0 cm), inject talimogene laherparepvec at different site for aiming uniform distribution in the following course.
- any previously uninjectable tumor(s) that is now injectable

Within the guidelines of the algorithm in Table 3 and the prioritization model above, each lesion should be injected with the maximum amount possible at each visit before moving on to the next lesion, subject to tumor-specific limitations (such as the inability to inject the full amount into the lesion). Lesions should be injected until the maximum volume per day (4.0 mL) has been reached or there are no further injectable lesions, whichever comes first.

Lesion site preparation

- Talimogene laherparepvec is to be administered only by intralesional injection into cutaneous, subcutaneous and nodal lesions with or without image ultrasound guidance. Talimogene laherparepvec must not be administered into visceral organ metastases.
- The injection site may be pre-treated with a topical anesthetic agent or an injectable local anesthetic; however, a local anesthetic must not be injected directly into the lesion. Please note that the anesthetic should not be mixed together with talimogene laherparepvec in the same syringe. Talimogene laherparepvec does not require any routine premedication.
- Swab the lesion and surrounding areas with alcohol, allow to dry.
- Talimogene laherparepvec is administered by HCP

Figure 4: Timeline of talimogene laherparepvec injection



* Talimogene laherparepvec is administered lower dose for the first course due to possible sero-negative status.
** Biopsy from local disease.
*** Biopsy from distant metastases if available or local disease of non-injection site (optional)

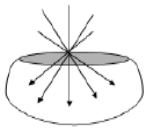
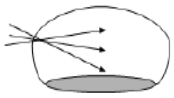
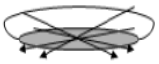
Table 3. Talimogene laherparepvec injection volume guideline based on tumor size

Tumor Size (longest dimension)	Maximum Injection Volume
> 5.0 cm	4.0 mL
> 2.5 cm to 5.0 cm	2.0 mL
> 1.5 cm to 2.5 cm	1.0 mL
> 0.5 cm to 1.5 cm	0.5 mL
≤ 0.5 cm	0.1 mL

6.2. Lesion injection

- All personnel handling talimogene laherparepvec or material contaminated with talimogene laherparepvec must observe safety precautions (e.g., wear a laboratory coat, safety glasses and gloves) in accordance with local/regional or BSL classification guidelines for administration.
- Inject talimogene laherparepvec intralesionally (Table 4.):
    a) A single point of insertion is recommended; multiple insertion points may be used if the tumor is larger than the radial reach of the needle.
    b) Talimogene laherparepvec should be injected along multiple different tracks within the lesion in order to obtain as wide a dispersion as possible.
    c) Distribute talimogene laherparepvec within the lesion through the insertion point using the radial reach of the needle in different directions to evenly distribute.
- Avoid premature extraction of the needle.
- After dosing, the injection site should be swabbed with alcohol and pressure should be applied with gauze for several seconds after injection.
- The injection site should be covered with an absorbent pad and dry occlusive dressing. Please ensure a fresh pair of gloves is worn when handling the absorbent pad and dressing to prevent cross contamination with talimogene laherparepvec. Please also ensure that the outside of the dressing is wiped down with an alcohol swab to further minimize any cross contamination.
- Discard materials used during injection (eg, gloves, needles, gauze) in accordance with local/regional or BSL classification guidelines.

Table 4. Schematic illustration of Talimogene laherparepvec injection

Thick lesion	Protruding lesion	Thin lesion
		

6.3. Dose management

Subjects should be assessed clinically for adverse events/toxicity prior to each dose using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Complete blood count with differential and chemistry panels including liver function laboratory tests (ALT, AST, and total bilirubin) should be obtained according to the schedule of assessment in the protocol, and

the results should be checked before each scheduled dose of talimogene laherparepvec. Dosing will occur only if these test values are acceptable per the protocol.

6.3.1 Dose Limiting Toxicities (DLTs)

Toxicity should be evaluated according to CTCAE version 4.0. DLTs should be defined based on CTCAE and should include events assessed as related to talimogene laherparepvec during treatment and up to 4 weeks after the last talimogene laherparepvec injection.

The following herpetic events are defined as DLTs:

- Serious herpetic events such as herpetic encephalitis, encephalomyelitis or disseminated herpetic infection.
- Any herpetic event confirmed related to talimogene laherparepvec that requires treatment with acyclovir or similar anti-viral agent, Talimogene laherparepvec treatment should be suspended if treatment is required with systemic acyclovir or other anti-virals, If ongoing treatment is required, talimogene laherparepvec treatment should be permanently discontinued. Herpetic events due to wild-type HSV-1 or wild-type HSV-2 which require acyclovir and are not due to talimogene laherparepvec (as confirmed by PCR testing) should not be considered as DLTs caused by talimogene laherparepvec
- Grade 3 or greater immune-mediated adverse events
- Any grade plasmacytoma at or near the injection site or evidence of impaired wound healing at the injection site
- Grade 3 or greater allergic reactions considered at least possibly related to talimogene laherparepvec
- Grade 4 non-hematologic toxicity.
- Grade 3 non-hematologic toxicity lasting > 3 days despite optimal supportive care;
  - Grade 3 fatigue will not be classified as DLT, irrespective of duration.
- Any Grade 3 or higher non-hematologic laboratory value if the abnormality:
  - fails to respond to medical intervention, or
  - leads to hospitalization, or
  - persists for > 1 week unless deemed not clinically important per both investigator and sponsor.
- Grade 3 or 4 febrile neutropenia.
- Grade 4 thrombocytopenia associated with a bleeding event deemed at least possibly related to talimogene laherparepvec and requiring intervention.
- Any other intolerable toxicity leading to permanent discontinuation of talimogene laherparepvec.
- Grade 5 toxicity (i.e. death).

If an unexpected DLT deemed at least possibly related to talimogene laherparepvec occurs, talimogene laherparepvec administration should be delayed until the DLT has resolved to at least CTCAE (v. 4.0) grade 1 or has returned to baseline.

All necessary supportive care shall be available to subjects. Additional treatment modifications should be considered depending upon the subject's clinical situation. Talimogene laherparepvec treatment should be continued based on the potential risk/benefit assessment of the subject.

6.3.2. Dose reduction

Dose reductions with regards to changes in the concentrations of talimogene laherparepvec are not permitted. However, patients may require a reduction in the volume injected due to a disease response or due to local toxicity at the injection site. However, if in the course of administration of talimogene laherparepvec the subject cannot tolerate the full dose due to an injection-related adverse event such as pain, the total volume given should be recorded, and the reason for intolerance should be documented as an adverse event.

6.3.3 Dosage Adjustments, Delays, Rules for Withholding or RestartingIf talimogene laherparepvec treatment was deayed by >2 week, that dose will be deemed to have been missed and the subject will proceed to the next scheduled treatment visit.

Dose reductions of talimogene laherparepvec is not permitted, other than a reduction in the volume injected due to a disease response.

If a subject experiences any of the following treatment-related toxicities, talimogene laherparepvec administration should be delayed until the toxicity has resolved to at least CTCAE grade 1 or baseline:

- Grade 2 or greater immune-mediated adverse events, with the exception of vitiligo.
- Grade 2 or greater allergic reactions.
- Any other grade 3 or greater hematologic or non-hematologic toxicity.

Subjects who are receiving talimogene laherparepvec may not receive systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir), but may receive a topically administered antiherpetic drug more than 20 cm from a talimogene laherparepvec injection site. Dosing should be permanently discontinued if, in the opinion of the investigator, the subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection).

If the subject requires corticosteroid dosing of >10 mg prednisone daily (or equivalent, eg, 1.5 mg dexamethasone) for any reason, talimogene laherparepvec dosing must be withheld until the corticosteroid dose has decreased to <10 mg prednisone daily (or equivalent).

Talimogene laherparepvec treatment should be continued based on the potential benefit/risk assessment of the subject.

If talimogene laherparepvec dosing is delayed by more than 6weeks from the date of the planned dose (i.e., approximately 8 weeks from the previous dose) due to the occurrence of an adverse event that is considered related to talimogene laherparepvec, the subject must be permanently withdrawn from talimogene laherparepvec treatment.

If talimogene laherparepvec dosing is delayed by more than 6 weeks from the date of the planned dose (i.e., approximately 8 weeks from the previous dose) for reasons other than treatment-related toxicity, the case must be reviewed by the principle investigator to determine if the subject can resume talimogene laherparepvec therapy.

Patient will be allowed to continue, capecitabine, hormonal therapy and/or anti-HER-2 therapy while receiving study drug.

6.4 Permanent Discontinuation of Treatment and Withdrawal of patients from study

Talimogene laherparepvec is to be permanently discontinued for patients meeting any of the following criteria:

- The patient, for any reason, requires treatment with another anticancer therapeutic agent for the study disease (other than the exceptions noted in the protocol, if applicable). In this case, discontinuation from the treatment occurs immediately upon the introduction of the new agent.
- Confirmed PDA grade 2 or greater Immune-mediated adverse events (with the exception of vitiligo) or allergic reactions attributed to talimogene laherparepvec that would require a dose delay of greater than 6 weeks from the date of the planned dose (i.e., approximately 8 weeks from the previous dose).
    - Note: immune-mediated glomerulonephritis, vasculitis, and pneumonitis and exacerbation of psoriasis have been observed in subjects receiving talimogene laherparepvec in clinical trials. Most of these subjects had a history of other autoimmune disease and/or prior treatment with agents that offered plausible alternative etiologies, however, immune-mediated adverse events can potentially involve any organ system.
- Any other talimogene laherparepvec-related non-hematologic or hematologic toxicities grade 3 or greater occur that, in the opinion of the investigator, would require a dose delay of greater than 4 weeks from the date of the planned dose (i.e., approximately 6 weeks from the previous dose).
- The subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection).
- A female subject becomes pregnant or fails to use acceptable method(s) of effective contraception (for those subjects who are able to conceive).
- A female subject breast feeds while on study treatment.
- Concurrent medical illness that, in the judgment of the investigator, would make continued treatment with talimogene laherparepvec dangerous for the subject.
- For additional information related special warnings and precautions for the use of talimogene laherparepvec please refer to the latest version of the Talimogene Laherparepvec Investigator's Brochure.
- Dosing noncompliance**:** If dosing compliance is not 100% (administration of talimogene laherparepvec on the scheduled date +/- 3 days in the absence of toxicity), the study treatment should be discontinued for the patient.
- Complete remission of locally recurrent disease with or without distant disease
- Patient withdraws consent. In the event that a patient withdraws consent, the reason(s) for withdrawal must be documented. Patients must be informed that their participation in the

study is voluntary and that they may choose not to take part in the study or to stop taking part at any time. If a patient chooses not to take part in the study or to stop at any time, his/her future medical care or medical benefits will not be affected.

6.5 The end of study

6.5.1. Definition of the end of the study

Previous talimogene laherparepvec single agent study showed that the median time to response was 4.1 months, and 50 % of these responders had progressive disease (PD) (defined by modified WHO criteria) prior to response. In this study talimogene laherparepvec administration will continue for at least 10 cycles (approximately 5 months) unless uncontrolled disease progression is observed. Beyond 10 cycles, progressive disease will be measured based on RECIST ver1.1.

6.5.2. Uncontrolled disease progression

Uncontrolled disease progression is defined as rapid growth of multiple measurable or non-measurable new lesions, or sum of the longest diameter of existing targeted lesions is >40% from the baseline.

Immunotherapeutic agents such as talimogene laherparepvec may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions

7.0. Pretreatment evaluation (within 6 weeks prior to study enrollment)

7.1. Informed consent/ patient registration

The study will be discussed with the patient, and any patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. A signed, Institutional Review Board approved, informed consent form must be obtained from patients before any study specific procedures or registration for study treatment can occur. All patients will be registered in the Clinical Oncology Research system.

7.2. Pretreatment evaluation

7.2.1. Complete medical history and physical examination including breast examination, vital signs, height, weight, demographics, and adverse events.

7.2.2. We will document concurrent medications as a standard of care but not for protocol purposes. Concurrent medications will not be included in the final analysis. However, we will

document and report any unexpected severe toxicity that is deemed to be related to the concurrent medication.

7.2.3. Documentation of ECOG PS, menopausal status, and date of last menstrual period.

7.2.4. The breast will be carefully and clinically measured, and the location of the involved area will be described. Location and size of the tumor, axillary and supraclavicular node status, and clinical TNM stage will be recorded. Locally recurrent breast tumors and skin lesions should be recorded with medical photography. Measurements should be bi-dimensional and expressed in centimeters.

7.2.5. Complete blood count (CBC), differential count, and platelet count;

7.2.6. Chemical profiles- simultaneous multichannel autoanalyzer (SMA) (Na, K, blood urea nitrogen (BUN), creatinine, Mg, calcium, AST, ALT, LDH, total bilirubin)

7.2.7. If a female patient is of childbearing potential, a urine or blood pregnancy test should be performed no more than 3 days before the start of treatment.

7.2.8. Levels of tumor markers (e.g., cancer antigen CA 27.29) will be assessed.

7.2.9. Chest x-ray.

7.2.10. PET/CT or chest and abdominal CT scan if clinically indicated.

7.2.11. Bone scan only if PET/CT is not performed.

7.2.12. Breast sonography with axillary assessment if clinically indicated

7.2.13. Ultrasound-guided core biopsy of local recurrence if samples (i.e., paraffin block or 5-10 unstained slides from the local recurrence) are not available. The imaging physician will perform the biopsy if indicated at MD Anderson.

7.2.14. HSV serology: serum HSV type 1 IgG.

7.2.15. Systemic immunity in serum or plasma levels of, IL-2, IL-12, TNF-alpha (α), IFN- alpha (α); and phenotype for T-cell subsets (CD3, CD4, CD8, CD25), and natural killer-cell subsets (CD16, CD56) will be determined via multiparameter fluorescence activated cell sorting (FACS) analysis (percentage and absolute numbers) in Dr. James Reuben's laboratory at MD Anderson.

7.2.16. Photography of the local recurrence in the chest wall.

8.0. Evaluation during study

The window for all assessments and treatments should be completed within 5 days of the scheduled time.

Patients will be allowed to continue current hormonal therapy, selected chemotherapy, targeted agents and/or anti-HER-2 therapy, which will be administered as standard of care, (per physician discretion) while receiving study drug.

8.1. Evaluation during talimogene laherparepvec:

8.1.1. Patients will have a CBC, differential count and platelet count before each cycle.

8.1.2. Patients may repeat the CBC, differential count and platelet count until recovery of these measures before the next cycle (absolute neutrophil counts ≧ 1,000 and platelets ≧ 100,000 per mm^3).

8.1.3. Medical history and physical examination with vital signs, weight, and PS before cycles 2 and 5 and every additional 2 cycles of treatments.

8.1.4. Digital photography of chest lesions before cycles 2, 5, and every additional 2 cycles of treatment.

8.1.5. Toxic effects will be assessed before each cycle.

8.1.6. SMA (Na, K, BUN, creatinine, Mg, calcium, AST, ALT, glucose, LDH, and total bilirubin) will be performed before each cycle.

8.1.7. Levels of tumor markers (e.g., cancer antigen CA 27.29) will be assessed before cycle 5 and every additional 4 cycles of treatment.

8.1.8. Systemic immunity in serum or plasma levels of GM-CSF, IL-2, IL-12, TNF-alpha (α), IFN- alpha (α); and phenotype for T-cell subsets (CD3, CD4, CD8, CD25), and NK-cell subsets (CD16, CD56) will be determined via multiparameter FACS analysis (percentage and absolute numbers) before cycle 5 and at the end of study in Dr. James Reuben's laboratory at MD Anderson.

8.1.9. PET-CT or CT of bone/ abdomen/chest should be performed before cycle 5 and before every additional 4 cycles of treatment as clinically indicated.

8.1.10. Disease assessment will be done at the end of cycle 4, cycle 8 and cycle 10.

8.2. Evaluation of distant metastases (before cycle 5)

If a patient has distant metastasis, every effort will be made to obtain tissues from an easily accessible metastatic site. If patient does not have distant metastasis or distant metastasis is not accessible, core biopsy of local lesions will be needed to collect tumor tissue. Every effort will be made to obtain biopsy tissue before cycle 5 for at least 60% of enrolled patients.
A pathologist collaborator will be notified before the biopsy and will handle the resected specimen. Every attempt will be made to identify any tumor change such as necrosis. Hematoxylin and Eosin staining will be performed with formalin-fixed paraffin-embedded

blocks to determine tumor, and immunohistochemical (IHC) staining will be made for immunity assessment. IHC assays will include CD3, CD4, and CD8 for T-cell immunity assessment, CD20 for B-cell immunity assessment, and CD16, CD56, and Granzyme B for NK cell immunity assessment. Cleaved caspase 3 staining for an apoptosis assay, Ki67 for a proliferation assay, and HSV antigen staining will be performed. If the remaining sample is ample, CD45RO, TIA-1, FoxP3, CD25, OX-40, CD56, CD57, CD1a, CD208, myeloperoxidase, CD68, COX-2, MHC Class I, and MHC Class II will also be assessed in Dr. Savitri Krishnamurthy's laboratory at MD Anderson.

8.3 Study Calendar

Evaluation and treatment	**Screening**	**Cycle 1 Day 1**	**Cycle 2 (D22+/-5 days)**	**Cycle 5 (D64 +/- 5 days)**	**Cycle 7 and every 2 cycles**	**Follow up[9]**
Time	**Baseline (within 6 weeks)**	**Prior to talimogene laherparepvec injection**				Patients will be monitored for 1 year after removal from the study or until death, whichever occurs first.
Eligibility, screening, consent, and registration	X					
Medical history	X					
Staging with tumor measurements	X					
Photography of chest wall	X[1]		X	X	X	
Biopsy of local recurrence [HE, IHC]	X[8]			X[8]		
Biopsy of easily accessible distant metastasis [HE, IHC]				X[8]		
Correlative immune study	X			X[7]		
Physical examinations, vital signs	X	X[2]	X	X	X	
ECOG PS	X	X[2]	X	X	X	
Hematology assessment and Biochemical profiles[3,5]	X	X[2]	X	X	X	
Tumor markers (CA27.29)[11], IgG (baseline only)	X			X	X[11]	
Chest X-ray; Breast sonography[13]	X					
Pregnancy test if applicable[10]	X					
PET-CT or CT scan of bone/ abdomen/chest as clinically indicated	X			X	X[4]	
Disease assessment [12]				X	X	

Adverse events[5]	X	X	X	X	X	
Talimogene Laherparepvec injection[6]		X	X	X	X	

1. Within 1 week prior to treatment
2. No need to repeat if within 7 days from baseline
3. Hematology include CBC, differential count and platelet count; and biochemical profiles SMA include Na, K, BUN, creatinine, Mg, calcium, AST, ALT, LDH, total bilirubin
4. Repeat every 4 cycles as clinical indicated
5. Before each cycle. Reporting exposure to talimogene laherparepvec and should be collected for the duration of the study and safety f/u
6. Starting cycle 2, Talimogene Laherparepvec injection will be given every 2 weeks until disease progression
7. Correlative immune study will be repeated before cycle 5 and at the end of study if available.
8. Core biopsy of local recurrence at baseline if samples (i.e., paraffin block or 5-10 unstained slides) from the local recurrence are not available. Core biopsy of either distant metastasis or local recurrent lesions before cycle 5 based on patient status.
9. a. Safety Follow-Up: should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. Safety Follow-Up Visit can be done in the clinic, or by phone if patient is not willing to come to the clinic for follow up.
   b. Unexpected AEs: Patients removed from study for unexpected adverse events will be monitored until AE is resolved or stabilized.
   c. Survival Follow-Up: approximately every 3 months patient survival information will be followed by chart reviewing, or by phone up to 1 year.
10. Female patients of childbearing potential must have a negative urine or blood pregnancy test no more than 3 days prior to starting study drug.
11. Tumor markers (CA 27.29) will be assessed at baseline, before cycle 5 and every additional 4 cycles of treatment. IgG and IgM will be tested at baseline only
12. Disease assessment will be performed at the end of cycle 4, cycle 8 and cycle 10
13. Breast sonography with axillary assessment if clinically indicated

Abbreviation; HE: hematoxilin and eosin staining, IHC: immunohistochemical staining,: talimogene laherparepvec

9.0. Criteria for response, overall response and disease control

Response must be evaluated using RECIST ver.1.1.Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (irrespective of scanner type) and magnetic resonance imaging (MRI) (*no less than double the* slice thickness *and a minimum of 10 mm*), 10 mm caliper measurement by clinical examination (when superficial), and 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Tumor lesions must be accurately measured in at least one dimension of local recurrence and skin metastases if applicable. These will be measured by caliper, and the extent of disease should be recorded on a photograph with a scale marker and injection marker. If these lesions are immeasurable, their extent should also be recorded on a photograph with a scale marker and injection marker to assess the rate of overall response.

9.1. Complete Response (CR): Disappearance of all target and non-target lesions at a minimum of 4 weeks.

9.2. Partial Response (PR): At least a 30% decrease in the sum of the longest diameter of the target lesions at a minimum of 4 weeks, taking as a reference the baseline sum of the longest diameter with target.

9.3. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as a reference the smallest sum of the longest diameter since the treatment started with target lesions.

9.4. Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). In the previous phase III melanoma study, PD (defined by modified WHO criteria) prior to response was observed in about 50% of responders, and median time to response was 4.1 months. Thus, for this study purpose, a true PD will be confirmed at the end of cycle 10 (approximately 5 months) as long as patients tolerated the treatment.

9.5. Criteria for Overall Response

Response definition among measurable and non-measurable disease combination. Overall response will be defined as a sum of the 3 response types.

	Non-measurable disease (i.e., bone)	Measurable disease (i.e., lung, liver, lymph nodes)
Type I measurable disease only	None	CR or PR,
Type II non-measurable disease only	CR,	None
Type III Both measurable and non-measurable disease	CR,	CR or PR,

A patient with PD of measurable disease prior to end of cycle 10 would be considered to have overall response if the PD is not confirmed at the end of cycle 10.

9.6. Criteria for Disease Control

Disease control definition among measurable and non-measurable disease combination

Controlled Disease	Non-measurable disease (i.e., bone)	Measurable disease (i.e., lung, liver, lymph nodes)
Type I measurable disease only	None	CR or PR, or SD ≥ 4 months or no true PD (at cycle10)
Type II non-measurable disease only	CR, or SD ≥ 4 M	None
Type III Both measurable and non-measurable disease	CR, or SD ≥ 4 M	CR or PR, or SD ≥ 4 months or no true PD (at cycle10)

A patient with PD of measurable disease prior to end of cycle 10 would be considered to have disease control if the PD is not confirmed at the end of cycle 10.

9.7. Response will not be considered evaluable in the following categories:

9.7.1. Early Deaths: Patients who die within the first 2 weeks of the initiation of drug therapy owing to concurrent disease. These cases will be considered treatment failures in the intent-to-treat analysis.

9.7.2. Lost to Follow-up: Patients for whom there is inadequate information to judge tumor response because of loss of contact with our institution (>2 months after a missed appointment) and with referring physician in spite of repeated attempts to locate them. These cases will be considered treatment failures in the intent-to-treat analysis.

9.7.3. Major Protocol Violation: Patients who significantly deviate from the treatment program by either adding or deleting another agent or another therapeutic maneuver or by modifying substantially the dosage and schedule of the drug under evaluation. Patients who do not fulfill the requirements outlined under Patient Eligibility are also included in this category.

9.8. Down staging is defined as a change in the tumor extent that results in reclassification of the primary tumor and/or regional lymph node metastases into a different (lower) T, N, or M subgroup.

9.9. All subjective toxic effects encountered during the study will be evaluated according to the CTCAE version 4.0. Objective toxic effects will be considered as the maximum numerical deviation from the normal range.

9.10. The survival of patients will be measured from the date of registration.

9.11. Patients will be monitored for 1 year after removal from the study or until death, whichever occurs first. Patients removed from study for unexpected adverse events will be monitored until AE is resolved or stabilized.

10.0. Investigational drug management

10.1. Prescription

Talimogene laherparepvec will be provided by Amgen Inc. and dispensed by the investigational pharmacy at MD Anderson.

10.2. Treatment compliance

The study drug must be dispensed only by an appropriately qualified person to patients in the study. The drug is to be used in accordance with the protocol by patients who are under the direct supervision of an investigator.

10.3. Packaging and labeling

Talimogene laherparepvec medication labels will comply with legal requirements.

10.4. Storage and accountability

Talimogene laherparepvec will be supplied to the pharmacy of the investigational site/institution by Amgen Inc. Talimogene laherparepvec should be stored away from light and according to the storage and expiration information (where required) provided on the label that is affixed to the package containing the investigational product. See detailed information in Appendices section 15.7 and/or the package insert in Appendix P in PDOL

The study drug must be stored in a secure area with limited access. It will be administered only to patients entered into the clinical study, at no cost to the patients, in accordance with the conditions specified in this protocol.

The investigational pharmacy will maintain accurate records of the dates and amounts of shipments of the study drug, recipients of the drug (patient-by-patient accounting), and any study treatment accidentally or deliberately destroyed. At the end of the study, the amount of study drug supplied, dispensed, and subsequently destroyed or returned to MD Anderson's investigational pharmacy must be reconciled. Used or expired study drug will be disposed per MD Anderson Cancer Center policy.

11.0. Safety monitoring and reporting

11.1. Adverse events

AEs will be assessed according to the CTCAE version 4.0 before each cycle. All study participants who have received any dose of talimogene laherparepvec will be evaluable for safety. Unexpected adverse events including laboratory adverse events deemed clinically significant by the investigator will be graded and recorded.

An AE is an undesirable medical occurrence (sign, symptom, or diagnosis) or worsening of a pre-existing medical condition (e.g., diabetes, congestive heart failure, rheumatoid arthritis) that occurs after the initiation of the investigational product, regardless of whether it is considered to be related to the investigational product. The worsening of an existing medical condition occurs when a condition that was present at baseline (e.g., cancer, diabetes, migraine headaches, gout) becomes more severe, more frequent, or increased in duration during treatment with the investigational product. Grade 2 or higher non-hematologic AEs and grade 3 or higher hematologic AEs will be recorded upon observation by the investigator or reported by the patient (regardless of whether they are attributed to investigational product), documented in the patient's medical record, and recorded in CORe. Grade 2 or higher abnormal lab values will be recorded as AEs; and grade 1 abnormal laboratory values will not be recorded as AEs, however, any clinical consequences of the abnormality and related grade 1 abnormality should be recorded as AEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of a central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as AEs. The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning attribution for each event for all subjects enrolled on the trial.

11.2. Serious adverse event (SAE) reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.
- The gene therapy reporting addendum ("Additional Reporting Form for Serious Adverse Events on Gene Transfer Trials") must be included with each SAE submitted.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

11.3 Investigator Communication with Amgen

11.3.1 Safety reporting to Amgen

The PI and the research team is responsible for compliance with expedited reporting requirements for serious and unexpected and related adverse events (SUSARs), for generation of SAE reports including narratives, and for periodic reporting to Amgen of SAEs as outlined in Table 5 and Table 6 below. Individual safety reports (Table 5) should be accompanied by the Fax Cover Form provided in Appendix 15.1, and sent to Amgen Global Safety, utilizing the fax or email information provided on the cover page. Aggregate safety reporting (Table 6) including listings, tabulations and summary reports should be scanned and accompanied by the Fax Cover Form provided in Appendix 15.5, and sent to Amgen NASCR, utilizing the email information provided on the cover page.

In addition to the requirements outlined in Table 5 and 6, Sponsor/Investigators are required to report direct exposures to talimogene laherparepvec (e.g., needle stick, splash back) of herpetic illness and all suspected herpetic events (refer to Section 11.3.2 'Accidental Exposures to Talimogene Laherparepvec and Herpetic Events').

MDA SAE form will be used for the reporting of these events. Anytime a report (i.e. herpetic, pregnancy, or lactation event) is submitted to Amgen (even though it may not be an SAE by definition), a copy must be provided to the IND Office at the same time.

Table 5. Expedited Reporting Requirements for Interventional Studies

Safety Data	**Timeframe for Submission to Amgen**
Suspected Unexpected Serious Adverse Reaction (SUSARs)	Individual reports sent to Amgen at time of expedited reporting to IRB and/or FDA.

Serious Adverse Events (SAEs) (related)	Individual reports sent to Amgen at time of expedited reporting to IRB and/or FDA
Pregnancy/Lactation	Individual reports sent within 10 days of Sponsor/Investigator awareness. (Refer to Appendix 15.3 and Appendix 15.4 for Amgen template forms)

Individual reports should be faxed to 1-888-814-8653 or scanned and sent via email to svc-ags-in-us@amgen.com

Table 6. Aggregate Reports

Safety Data	**Timeframe for submission to Amgen**
Adverse events (all serious and non-serious adverse events, regardless of relatedness)	Line listing and summary tabulation of **all** adverse events sent annually AND at end of study
US IND Annual Safety Report	Annually
Other Aggregate Analyses (any report containing safety data generated during the course of the study)	At time of ISS sponsor submission to anybody governing research conduct (e.g., RA, IRB, etc.)
Final (End of Study) Report, including: □ Unblinding data for blinded studies □ Reports of unauthorized use of a marketed product	At time of ISS sponsor submission to anybody governing research conduct (e.g., RA, IRB, etc.) but not later than 1 calendar year after study completion

Aggregate reports should be submitted via email to the Amgen NASCR manager, accompanied by the Fax Cover Form in Appendix 15.5

Please refer to the ICH Guidelines E2A for safety related definitions and terminology: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf.

11.3.2 Accidental Exposures to Talimogene Laherparepvic and Herpetic Event Reporting

In order to better assess and understand the potential risks to treated patients and/or third parties following the treatment of clinical trial subjects with talimogene laherparepvec, special reporting procedures apply for accidental exposures to talimogene laherparepvec and for suspected herpetic events. See Table 7 for a summary of reporting requirements. Clinicians should review the Imlygic package insert (available online) for additional information on the safe handling of talimogene laherparepvec.

Accidental Exposure of HCPs to Talimogene Laherparepvec

HCPs involved in your clinical trial who were directly exposed to talimogene laherparepvec (e.g., needle stick, splash back) but who are without signs or symptoms of herpetic illness should be reported to Amgen at 1-855-IMLYGIC (1-855-465-9442).

Suspected Herpetic Events

Suspected herpetic events must be reported to Amgen within 24 hours of awareness. Reporting is required for: (1) suspected herpetic events in treated patients; (2) suspected herpetic events in at risk HCPs with direct or indirect exposure and (3) suspected herpetic events in treated patient's close contacts, as outlined in Table 7. An example of the Suspected IMLYGIC™ (Talimogene laherparepvec) or Herpes Virus Associated Adverse Event can be found in Appendix 15.2.

In addition to reporting these events, suspected herpetic lesions should be swabbed and submitted for qPCR testing for the detection of talimogene laherparepvec. Samples should be collected using appropriate technique and a flocked swab from site supplies. This test is likely to be more reliable if performed within the first three days of symptom appearance, however, all lesions should be swabbed, regardless of the timing of presentation. Amgen does not require qPCR or other testing for wild type HSV-1.

- **Reporting Process for ISS Treated Patients:**

  - Any suspected herpetic lesion should be reported to Amgen at 1-855-IMLYGIC (1-855-465-9442), evaluated by the Sponsor/Investigator and swabbed for qPCR testing.

  - Once an initial report has been made, additional materials will be provided, including reporting forms and supplies needed for shipment of swab samples. Amgen will require patient consent for qPCR testing, which must be obtained prior to swabbing.

- **Reporting Process for HCPs and Close Contacts:**
  Sponsor/Investigator should advise any HCPs and/or Close Contacts with suspected herpetic lesions to contact their personal physician to facilitate reporting to Amgen. Suspected herpetic lesions can be reported by the Sponsor / Investigator, personal physician or exposed individual to Amgen at 1-855-IMLYGIC (1-855-465-9442). Once an initial report has been made, additional materials will be provided, including reporting forms and supplies needed for the shipment of swab samples. Amgen will require patient consent for qPCR testing, which must be obtained prior to swabbing.

Table 7. Accidental Exposure & Herpetic Event Reporting Requirement Summary

Exposed Person	Reporter	Timeframe for Reporting to Amgen	Report Mechanism	Timing of Swab Collection	qPCR Testing?	Responsible Party for Lesion Swabbing	qPCR Test Result Distribution*
Treated Patients **with suspected herpetic lesions**	Sponsor / Investigator	Within 24 hours of Sponsor / Investigator awareness	Contact Amgen at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions (ideally within 3 days of appearance of symptoms)	Yes, if consent obtained	Sponsor / Investigator	Sponsor / Investigator and Amgen

HCP directly exposed to product (e.g., needle stick, splash back) without signs or symptoms of herpetic illness	HCP's Personal Physician or impacted person	Within 24 hours of Reporter awareness	Contact Amgen at 1-855-IMLYGIC (1-855-465-9442) to report event	N/A	N/A	N/A	N/A
HCP directly or indirectly exposed to product **with suspected herpetic lesions**	HCP's Personal Physician or impacted person	Within 24 hours of Reporter awareness	Contact Amgen at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions (ideally within 3 days of appearance of symptoms)	Yes, if consent obtained	HCP or HCP's Personal Physician	HCP's Personal Physician and Amgen
Close Contact (eg caregiver, spouse, child) **with suspected herpetic lesions**	Sponsor / Investigator, Close Contact's Personal Physician or Close Contact	Within 24 hours of Reporter awareness	Contact Amgen at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions (ideally within 3 days of appearance of symptoms)	Yes, if consent obtained	Sponsor / Investigator, Close Contact's Personal Physician	Sponsor / Investigator, Close Contact's Personal Physician and Amgen

*The laboratory conducting the qPCR testing on behalf of Amgen is Viracor.

12.0. Data management

12.1. Data collection and entry

Data collected from the study will be entered in PDMS or CORe.

The Principal Investigator is responsible for assuring that the data entered into the database are complete and accurate and that data entry is performed in a timely manner.

Demographic information, age, sex, race, and date of birth; date of initial breast cancer diagnosis, surgery, local recurrence, and distant metastases if indicated; end date of chemotherapy including targeting agents, radiation therapy, or hormone therapy; menopausal status; clinical and pathologic stage of initial breast cancer; initial tumor histology, nuclear grade, estrogen receptor status, progesterone receptor status, and HER2 status; lymphatic invasion, vascular invasion, and tumor margins; previous chemotherapy regimens including targeting agents, type of surgery, and type of radiation therapy, hormone therapy, etc.; date of treatment, treatment response, levels of overall response, and AEs [>/=2 non-hematologic and >/=3 hematological AEs] will be collected. Grade 2 or higher abnormal lab values will be recorded as AEs; and grade 1 abnormal laboratory values will not be reported as AEs; however, any clinical consequences of the abnormality should be reported as AEs. Concomitant medications will not be entered in the case report form, captured only in the medical record.

12.2. Data confidentiality plan

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity will be possible only after accessing a password-protected database. Access to the database will be available only to individuals directly involved in the study.

Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

13.0. Statistical consideration

13.1. Statistical design

The primary objective of this phase II trial is to assess the efficacy of talimogene laherparepvec as a single agent in locally recurrent IBC and non-IBC patients. The primary endpoint is the rate of overall response.

The overall response rate is defined as the percentage of CR, PR in overall patients. Patients will be evaluated for disease control at the end of cycle 4 (2 months), cycle 8 (4 months) and cycle 10 (5 months). If patients have measurable disease only and achieve CR or PR, they will be considered Response Type I. If patients have non-measurable disease only, and achieved CR, they will be considered as Response Type II. If patients have both measurable and non-measurable disease and achieve CR or PR at the measurable disease sites, and achieved CR at the non-measurable disease site, they will be considered as Response Type III. If patients have mixed responses such as progression of measurable disease and no progression of non-measurable disease at 5 months or vice versa, they will be considered to have uncontrolled disease. The Overall Response rate will de defined as a sum of the 3 response types.

The trial will be conducted using a two-stage design and the overall response rate will be estimated accordingly. It is assumed that the talimogene laherparepvec single agent will have a response rate of 20%. A response rate of 5% or lower will be considered treatment failure and the regimen will be rejected under this circumstance. 13 patients will be enrolled to the first stage. The study accrual will be delayed until all 13 patients are evaluable for reponse. A summary report will be submitted to the medical monitor in the IND office. If no patients achieve an overall response to the treatment, the trial will be stopped and the regimen will be declared as ineffective. If there are 1 or more patients achieve an overall response, 22 more patients will be enrolled to the study to reach a total of 35 treated patients. By the end of the study, the new regimen will be rejected if less than or equal to 3/35 patients achieve overall response and will not be considered worthy of further investigation otherwise.

We have reviewed the 8 patients treated thus far, and determined that 1 of those 8 patients would not be eligible per the current proposed revised criteria due to extensive (≥5% Total Body Surface) skin lesion and will be replaced. As such, the overall sample size will be increased to 36 by one more patient. The afore mentioned one patient that is still evaluable for toxicity and efficacy in the overall end analysis, but not as a part of the evaluation for the 13 patients treated in the first stage. The above two-stage design statistical analysis plan will not change.

The operating characteristics of the trial are given as follows. When the true response rate is 5% the probability of stopping the trial early is 51% and the probability of claiming the regimen to be promising is 8.4%. On the other hand, if the response rate is 20%, the probability to stop the trial early is 5% and the probability of claiming the regimen to be promising is 90%. The

expected sample sizes are 23.7 and 33.8 when the true overall response rates are 5% and 20%, respectively

We will monitor severe toxicity, grade 3 or greater possibly, probably or definitely treatment related toxicities with CTCAE ver.4.0, by cohorts of 5 patients for the whole patient population (N=36) for the first cycle. A summary report will be submitted to the medical monitor in the IND office. The stopping boundary is calculated based on the beta-binomial distribution. We assume that number of patients who develop severe toxicity follows a binomial distribution with probability p, and p has a prior distribution of beta (0.20, 0.80). We consider that the probability of severe toxicity greater than 20% is excessive to the patients. The stopping boundary is chosen to stop the trial if the data indicate that there is a high probability that excessive toxicity-i.e., probability (p>0.20|data) ≧90%. The trial will be stopped and the treatment will be considered too toxic if the number of patients with severe toxic effects exceeds >=3/5, 4/10, 6/15, 7/20, 8/25, 10/30, and 11/35 for the first cycle. The operating characteristics are provided, based on 5,000 simulations. For example, if the true toxicity rate is 10%, the probability to stop the trial early due to toxicity is very low, 2% and an average of 34.5 patients will be treated on trial. On the other hand, if the true severe toxicity rate is 30%, the probability of stopping the trial early would be 62% with an average of 21.5 patients treated. When the true severe toxicity rate is 20%, we will have a 21% chance of terminating the trial early with an average of 30.3 patients treated. However if the toxicity rate is as high as 40%, then we will have a 91% chance to stop the trial early and with an average of only 13.5 patients treated.

Secondary objectives includes determining the overall disease control rate, local overall response rate and disease control rate, PFS, and OS in all patients; the local overall response rate and disease control rate, PFS, and OS in patients without distant metastases; and the local overall response rate and disease control rate, PFS, and OS in patients with distant metastases for defining the local efficacy of talimogene laherparepvec injection among breast cancer patients with inoperable local recurrence after surgery. In addition, this includes safety and tolerability of talimogene laherparepvec in these patients. The definition of PFS is time from treatment initiation until disease progression or death and this progression needs to be confirmed after the end of cycle 10. For example, patients who showed progress at 2 months but responded as PR at 5 months, we determine this as PR. In contrast, patients who showed progress at 2 months and was confirmed PD at 5 months, we determine this as PD at 2 months. The definition of OS is time from treatment initiation until any cause of death.

Analysis plan:

By the end of the study, the overall response rate will be estimated with 95% confidence intervals for all evaluabe patients and for patients with or without distant metastasis, separately. PFS and OS from registration will also be estimated using Kaplan-Meier method with 95% confidence intervals.

Biomarker endpoints will be measured in tissue and in surrogate blood or plasma before and after the treatment. Correlation between biomarkers from various markers and between tissue and blood/plasma will be assessed by Pearson or Spearman rank correlation coefficients for

continuous biomarkers and by chi-square or Fisher's exact test for discrete covariates. The associations between markers or change in the level of markers and overall response status will first be assessed graphically and then tested using a t-test/analysis of variance or Wilcoxon rank sum test/Kruskal-Wallis test, when appropriate. Repeated measures analysis including mixed effects modeling will be performed to analyze biomarkers change over time. We may also evaluate the association between the changes in the level of marker and the overall response status.

13.2 Primary endpoint

The rate of overall response for measurable and immeasurable disease in all patients.

13.3. Secondary endpoints

13.3.1. overall disease control rate, PFS, and OS in all patients

13.3.2. Local overall response rate and disease control rate, PFS, and OS in all patients.

13.3.3. Local overall response rate and disease control rate, PFS, and OS in patients without distant metastases.

13.3.4. Local overall response rate and disease control rate, PFS, and OS in patients with distant metastases.

13.3.5. Toxicity

14.0. Reference

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15.0 Appendices

15.1 Sample Fax Cover Sheet for Individual Safety Reports (Amgen Global Safety)

<<LSO/SOPS - enter Form Type>>
Investigator Sponsored Study
Amgen ISS <<LSO/SOPS - Select Category>>
FAX Transmittal Form
<<LSO/SOPS - Enter Product>>

<<LSO/SOPS - Enter Amgen Study Number>> / <<LSO/SOPS - Enter Sponsor Study ID, if applicable. If none, delete line>>

To: Amgen Global Safety, <<LSO/SOPS - Enter Location>> Phone No: <<LSO/SOPS - enter Local Phone # or N/A for US>> Fax No: <<LSO - enter Local Fax # >> <<SOPS - select Fax #>>	**AMGEN ISS PROTOCOL #:**_____ Sponsor: <<LSO/SOPS - Enter Institution Name>> Sponsor Contact Name: _____ Fax No:_____ Phone No:_____ Date: _____

Use this form as a cover page for an individual report, for batched individual reports, and for line listings.
******NOTE: Please use data reconciliation fax cover sheet to submit data reconciliation line listings.***

Fax transmission contents (Check all that apply):

To be sent immediately after each single case submission to RA, EC, IRB or DMC:

☐ Expeditable Serious Adverse Events/Serious Adverse Drug Reactions # of Reports Submitted: _____

To be sent in regular intervals per contractual agreement (eg, as batched individual reports or line listings):

☐ Serious Adverse Drug Reactions # of Reports Submitted: _____
Period from _____ to _____
DD/MMM/YYYY DD/MMM/YYYY

☐ Serious Adverse Events # of Reports Submitted: _____
*(does **NOT** apply for marketed Amgen products)*
Period from _____ to _____
DD/MMM/YYYY DD/MMM/YYYY

Other Reports (to be sent as per contractual agreement eg, pregnancy/lactation reports)

☐ Specify type of report: _____ # of Reports Submitted: _____
Period from _____ to _____
DD/MMM/YYYY DD/MMM/YYYY

For multi-country studies please indicate countries of transmitted report(s) origin:

Total # of pages in this transmission, including cover page: _____

Version date 01May2013

15.2 Sample of Report Form for Herpetic Event with Accidental Exposure of Close Contact or HCP to Talimogene Laherparepvec

AMGEN 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 7c above) at the time of the event?

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

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

AMGEN Study # 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):			____/___/_______	

AMGEN 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: _____

AMGEN 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

15.3 Sample of Pregnancy Notification Worksheet

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:** _____

****

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011

Page **1** of **1**

15.4 Sample of Lactation Notification Worksheet

Print Form

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 maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2.

Page **1** of **1**

15.5 Sample Fax Cover Form for Aggregate Safety Reporting

Aggregate Safety Reporting
Investigator Sponsored Study (ISS)
FAX Transmittal Form
Imlygic (Talimogene Laherparepvec, T-VEC)

To: NASCR Study Management **Email: <<NASCR Manager >>**	**AMGEN ISS PROTOCOL #:**_____ Sponsor: _____ Sponsor Contact Name: _____ Fax No:_____ Phone No:_____ Date: _____

Use this form as a cover page for all aggregate safety reporting

Fax transmission contents (Check all that apply):

Description of Reports

- ☐ **Adverse Event Line Listing**
  (all serious and non-serious events, regardless of relatedness)
- ☐ **Adverse Events Summary Tabulation**
  (all serious and non-serious events, regardless of relatedness)
- ☐ **US IND Annual Report, Date:**_____
- ☐ **Other Aggregate Analyses (please specify:**_____**)**
- ☐ **End of Study Final Report**
- ☐ **Other (please specify:**_____**)**

Total # of pages in this transmission, including cover page: _____

15.6 The Rule of Nines

Guide that will be used to calculate the percentage of total body surface area (TBSA) of skin disease involvement. See figure 1 below.

- Head/neck - 9%
- Each arm - 9%
- Anterior thorax - 18%
- Posterior thorax - 18%
- Each leg - 18%
- Perineum - 1%
- A patient's palm is approximately 1% and can be used for estimating patchy areas

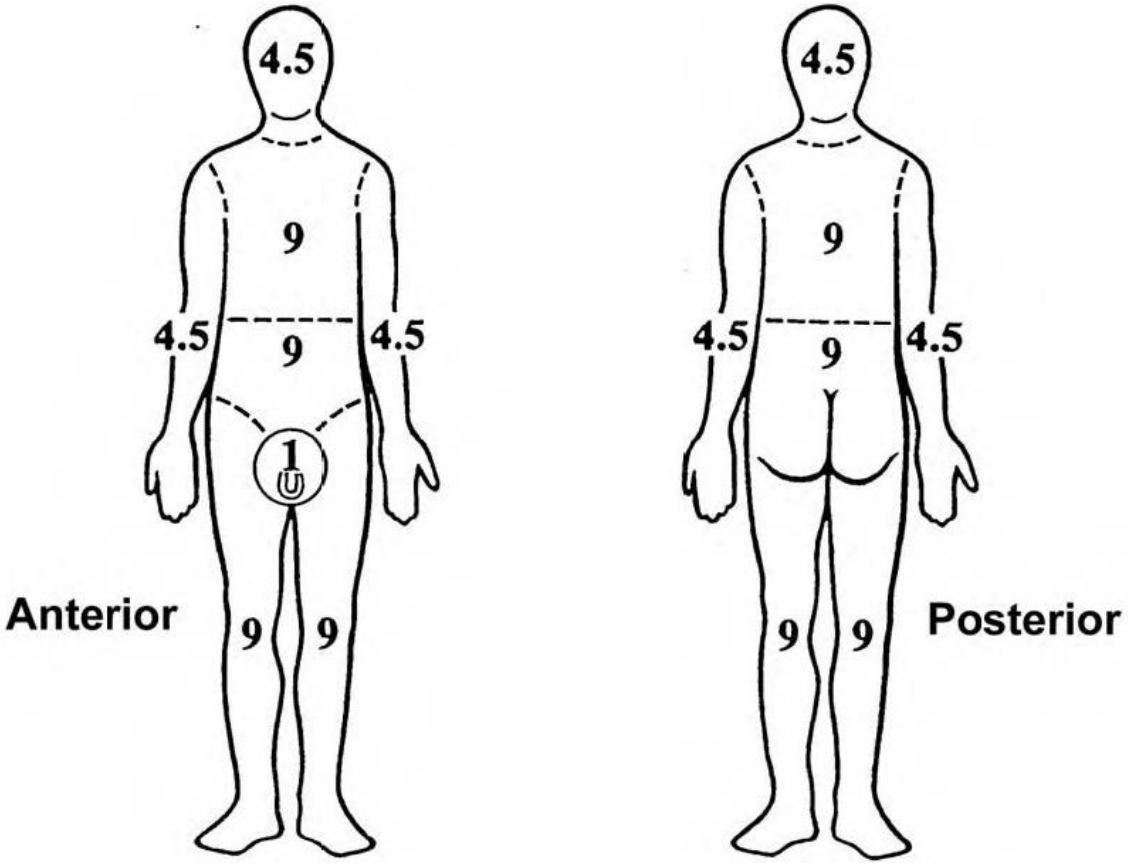
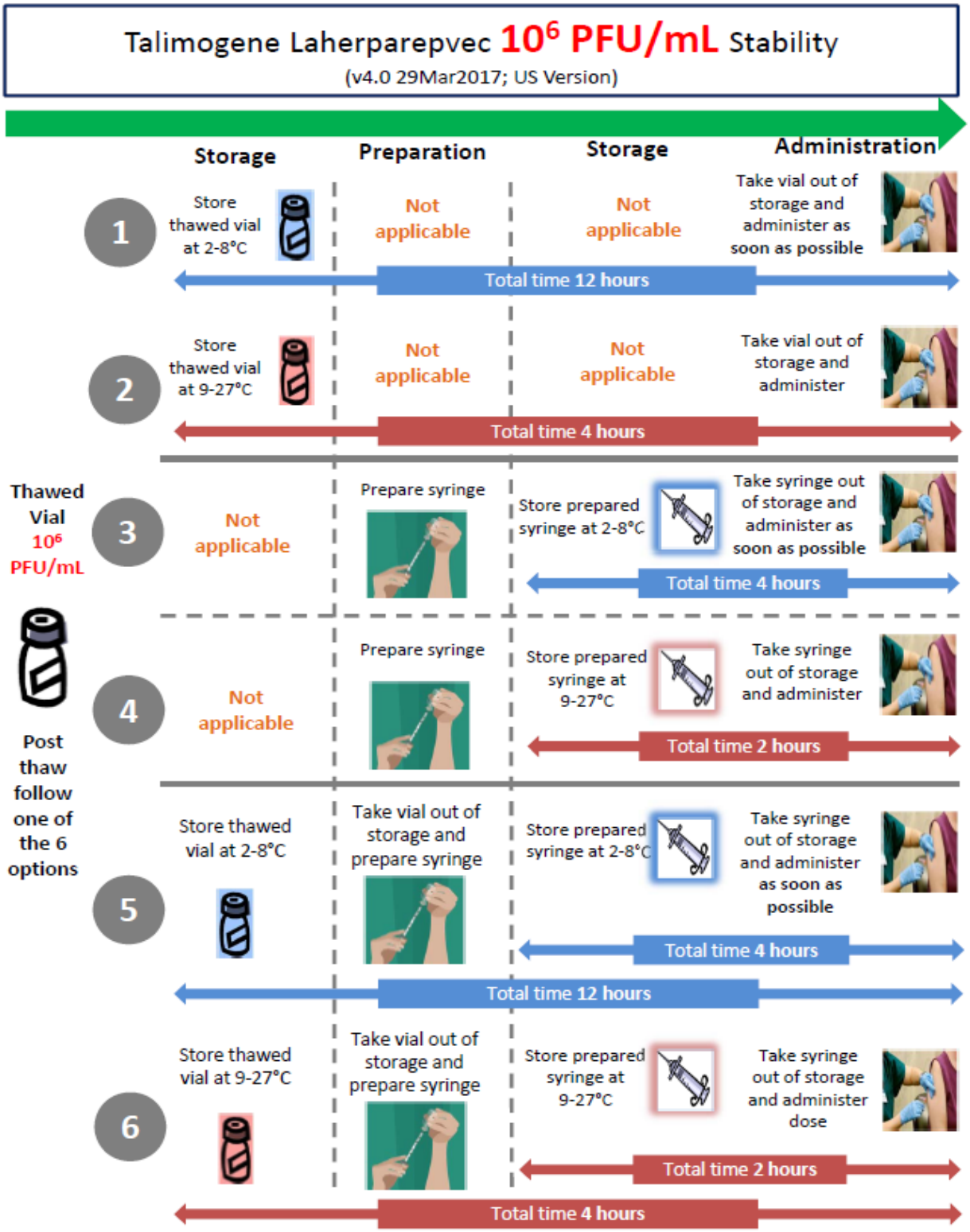
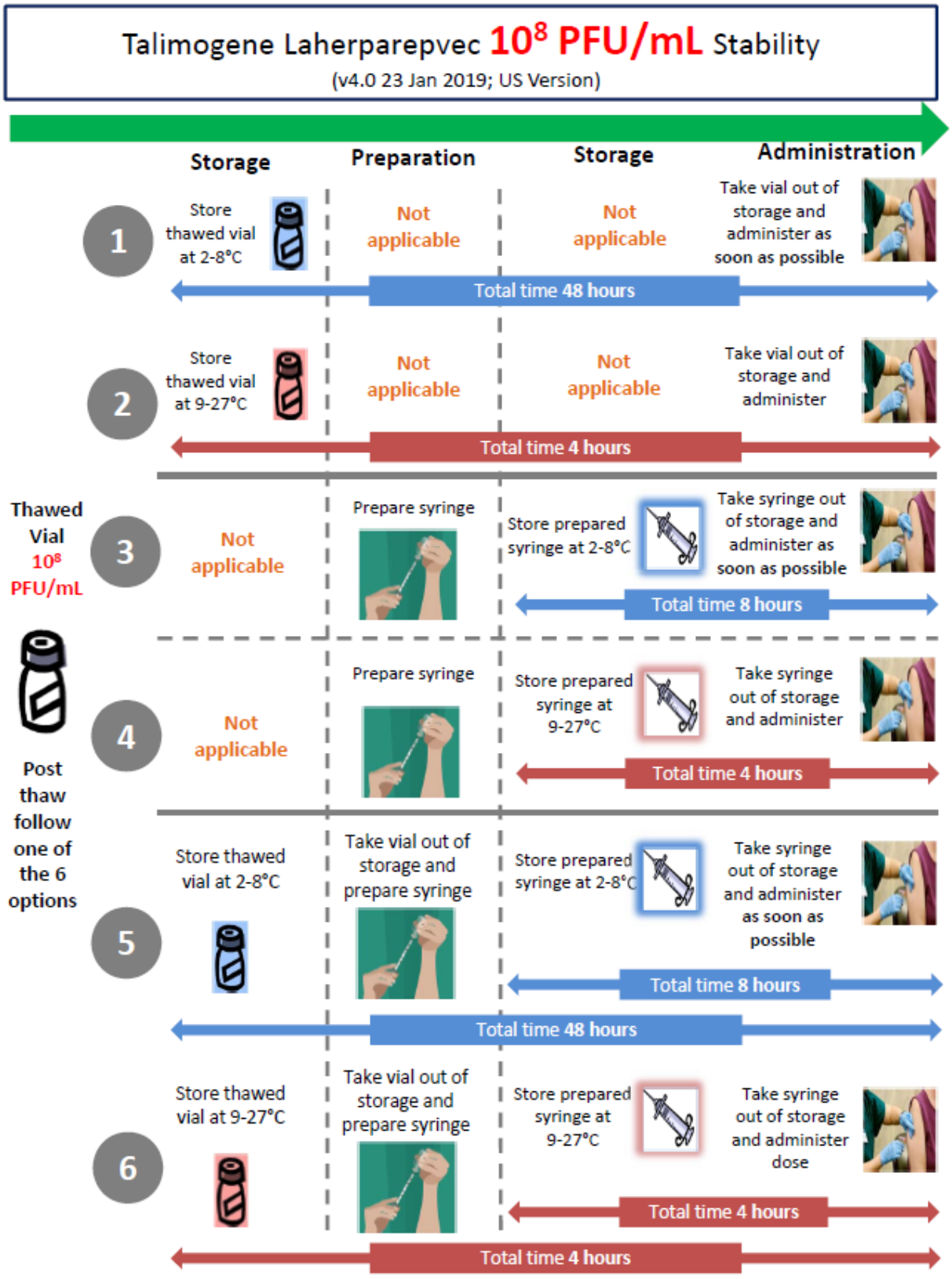


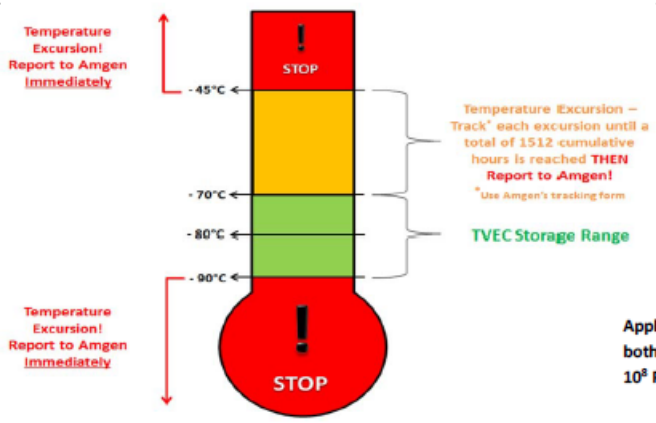
Figure 1. Rule of Nines

15.7 Talimogene Laherparepvec Storage and Handling




Talimogene Laherparepvec 10⁸ PFU/mL Stability
(v4.0 23 Jan 2019; US Version)
Storage
Preparation
Storage
Administration
Thawed Vial 10⁸ PFU/mL
Post thaw follow one of the 6 options
1
Store thawed vial at 2-8°C
Not applicable
Not applicable
Take vial out of storage and administer as soon as possible
Total time 48 hours
2
Store thawed vial at 9-27°C
Not applicable
Not applicable
Take vial out of storage and administer
Total time 4 hours
3
Not applicable
Prepare syringe
Store prepared syringe at 2-8°C
Take syringe out of storage and administer as soon as possible
Total time 8 hours
4
Not applicable
Prepare syringe
Store prepared syringe at 9-27°C
Take syringe out of storage and administer
Total time 4 hours
5
Store thawed vial at 2-8°C
Take vial out of storage and prepare syringe
Store prepared syringe at 2-8°C
Take syringe out of storage and administer as soon as possible
Total time 8 hours
Total time 48 hours
6
Store thawed vial at 9-27°C
Take vial out of storage and prepare syringe
Store prepared syringe at 9-27°C
Take syringe out of storage and administer dose
Total time 4 hours
Total time 4 hours

Talimogene Laherparepvec Storage and Clinical Handling Temperature Excursion Management

Stage or Clinical Handling?	Is temperature monitoring required?	Do I need to report temperature excursions to Amgen?	
Storage	**Yes** Please monitor and record temperatures on Amgen specified document (for review by clinical monitor)	**Yes** Please report using Amgen's temperature excursion report form	
Clinical Handling	**Yes** Please monitor and record temperature per local standards (not reviewed by local monitor)	**No** If temperature excursion is observed then discard product and start again	See table below

Thaw Requirement	Total storage time for thawed T-VEC/Placebo			
15°C to 30°C (59°F to 86°F)	2°C to 8°C (36°F to 46°F)		Up to 25°C (80°F)*	
10^6 & 10^8 PFU/mL	10^6 PFU/mL	10^8 PFU/mL	10^6 PFU/mL	10^8 PFU/mL
Thaw protected from light until fully liquid (approx. 30 minutes at the stated temperature range). Do not expose vials to higher temperatures. Do not refreeze thawed T-VEC.	**12 hours** (inclusive of **4 hours** maximum in the syringe)	**48 hours** (inclusive of **8 hours** maximum in the syringe)	**4 hours** (inclusive of **2 hours** maximum in the syringe)	**4 hours** (inclusive of **4 hours** maximum in the syringe)

Please refer to the T-VEC Stability diagrams for further details. *This covers temperatures from 9°C to 27°C (48°F to 80°F)

Version 5.0 US Only 23 Jan 2019