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A Single Arm Phase 2 Study of talimogene laherparepvec in patients with cutaneous squamous cell cancer

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Investigator Agreement

I have read, understand and will adhere to the protocol as written, that any changes to the protocol will be approved by the sponsor or sponsor-investigator and the IRB, except changes to eliminate an immediate hazard to study subjects.
I agree to conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, FDA regulations, local IRB and legal requirements.

_____ 7/5/2023

Signature Date (MM/DD/YY)

Clara N. Curiel, MD

_____

Name of Principal Investigator

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1. INTRODUCTION / SYNOPSIS

1.1 Phase

This is a Phase 2, single center study to treat low risk cutaneous squamous cell carcinomas (cSCC).

1.2 Indication

- Clinically consistent squamous cell carcinomas of the keratoacanthoma type and/or histologically confirmed other type of well-differentiated, low risk cSCC measuring > 0.5 cm to < 5 cm.

- Participants with cSCCs that are:
  - Low risk, according to Brigham and Women Hospital's Tumor Staging(1) and the American Joint Committee on Cancer (Table 3),
  - "Unresectable" based on a series of clinical scenarios that include:
    1. Presence of co-morbidities that significantly influence the capacity of the patient to tolerate surgical procedures (e.g. significant stasis/edema in lower extremities lesions, patients predispose to wound dehiscence, etc.); and
    2. Participant with multiple cSCCs that increase the surgical burden of complications or tolerance for these repeated procedures
    3. Recurrent cSCC lesions after surgical intervention in areas where radiation treatment might be associated with increased complications
    4. Participant declines surgery or other standard treatments for cSCC
- In the setting of study participants with tumor multiplicity, a maximum number of 3 cSCCs may be treated per anatomical site. In this clinical setting, the tumors will be required to be at least be 10 cm apart.

1.3 Endpoints

Primary Endpoint

The primary end point is to evaluate the overall response rate (ORR) defined as proportion of subjects who achieved complete response (CR) and partial response (PR) in the cSCC Target injected lesions (TILs).

Secondary Endpoints

1. Safety and adverse effect profile of talimogene laherparepvec in cSCC.
2. To measure time of response in cSCC TILs.
3. To measure the duration of overall response (DOR) of TILs.

4. Assess durable response rate (DRR) of TILs.
5. To measure the time to progression (TTP) of TILs.
6. Overall response rate (ORR) (CR+PR) assessed by imaging technique (high frequency ultrasound). This endpoint only applies to patients enrolled at the University of Arizona Cancer Center.
7. Overall clinical response rate (CR+PR) of individual TILs with talimogene laherparepvec (not as overall subject response).
8. Overall clinical response rate (CR+PR) in cSCC Target non-injected lesion(s) (TNILs).

Exploratory Endpoint

The exploratory endpoint is to evaluate the abscopal effect of TVEC by determining the frequency of non-melanoma skin cancers 24 months prior to the TVEC injections (or Visit 1), 12 months prior to the TVEC injections (or Visit 1), as compared to the frequency of non-melanoma skin cancers 12 months after the TVEC injections (or Visit 4) and then 24 months after the last injection (or Visit 4) if available.

1.4 Patient Population

The patient population for this study will be non-immunocompromised patients presenting with at least one eligible cSCC. The TILs should be located in anatomical sites other than head and neck.

2. STUDY DESIGN

2.1 Phase

This is a Phase 2, single site, single arm study. All subjects enrolled in the study will be treated with talimogene laherparepvec.

2.2 Number of centers

There are two participating sites for this study: The University of Arizona Cancer Center and Honor Health Research Institute.

2.3 Number of subjects

There will be approximately 20 subjects participating in this protocol.

2.4 The subject participation time period

The subject participation period will be approximately 48 weeks. This will include a screening visit, 4 injection visits and 5 follow up visits. Total length of study/patient is 8.5 to 10.5 months.

Table 1. Visit Schedule

Screening Visit/V0

Selection of study TILs. Low-risk cSCC with at least 1 lesion > 0.5 cm to < 5 cm. TILs will have partial biopsies for confirmatory diagnosis. A total of up to 5 TILs per subject can be selected for treatment with no more than 3 lesions in one anatomical area. TILs in the same anatomical area will need to be 10 cm apart from the other injected lesions. A high frequency ultrasound of the TILs will be performed at baseline prior to starting first injection.

Selection of study TNILs. Lesions that are clinically suspicious of cSCC in the same anatomical location as TILs. Up to 10 TNILs can be followed with no more than 2 TNILs selected in the same anatomical area as a TIL. TNILs will have partial biopsies for confirmatory diagnosis. TNILs will be assessed by clinical measurement only without the use of ultrasound technique.

Visit 1: First Injection Visit: One to four (1-4) weeks after V0

- Target lesions (TILs and TNILs) are identified and documented with measurements and photographs. Photographs will be taken with regional and close up view of the anatomical area and lesion (Appendix A).
- Inject 0.1ml – 4ml (based on TILs size – section 7.1, Table 5) Talimogene laherparepvec at nominal concentration of 10^6 plaque forming units (PFU)/mL with approximately 1.15 mL in a 2 mL vial for the initial dose. This will be administered intralesionally to 1-3 cSCC lesions per anatomical site with a maximum of 5 injectable lesions per patient.

Visit 2: Second injection visit: Three (3) Weeks after V1

- Target lesions are identified and documented with measurements and photographs. Photographs will be taken with global and close up view of the anatomical area and lesion (Appendix A).
- Inject 0.1ml – 4ml (based on TILs size) and number of lesions selected. Talimogene laherparepvec at nominal concentration of 10^8 PFU/mL with

approximately 1.15 mL in a 2 mL vial for the second and subsequent doses.

Visit 3: Third injection visit: Two (2) Weeks after V2

- Target lesions are identified and documented with measurements and photographs. Photographs will be taken with global and close up view of the anatomical area and lesion.
- Inject 0.1ml – 4ml (based on TILs size) and number of lesions selected. Talimogene laherparepvec at nominal concentration of 10^8 PFU/mL with approximately 1.15 mL in a 2 mL vial for the subsequent doses.

Visit 4: Fourth injection visit: Two (2) Weeks after V3

- Target lesions are identified and documented with measurements and photographs. Photographs will be taken with global and close up view of the anatomical area and lesion (Appendix A).
- Inject 0.1ml – 4ml (based on TILs size) and number of lesions selected. Talimogene laherparepvec at nominal concentration of 10^8 PFU/mL with approximately 1.15 mL in a 2 mL vial for the subsequent doses.

Visit 5: First Follow up visit: Four (4) weeks after V4

- Target lesions are identified and documented with measurements and photographs. Photographs will be taken with global and close up view of the anatomical area and lesion (Appendix A).

Visit 6: Second Follow up visit: Four (4) weeks after V5

- Target lesions are identified and documented with measurements and photographs. Photographs will be taken with global and close up view of the anatomical area and lesion (Appendix A). A repeat high-frequency ultrasound of target lesions will be completed to assess response from baseline.

Visit 7: Third Follow up visit: Six (6) weeks after V6

- Target lesions are identified and documented with measurements and photographs. Photographs will be taken with global and close up view of the

anatomical area and lesion (Appendix A).

Visit 8: Fourth Follow up visit: Fourteen (14) weeks after V7

- Target lesions are identified and documented with measurements and photographs. Photographs will be taken with global and close up view of the anatomical area and lesion (Appendix A).

Visit 9: Telephone Follow up: twelve (12) months after first injection (V1)

- Research coordinator will assess patient over the phone to determine if any changes have occurred to target lesions after V8.

3. OBJECTIVES

3.1 Primary Objective

1. To evaluate the ORR, defined as the proportion of subjects who achieved CR and PR in the cSCC TILs.

3.2 Secondary Objective

1. To assess the safety and adverse effect profile of talimogene laherparepvec in low risk cSCC. This will be determined by incidence of all adverse events (AEs), grade ≥ 3 AEs, safety adverse events (SAEs), and events requiring the discontinuation of study drug, local effects on the tumor (ie, pain, inflammation and ulceration), and any clinically significant laboratory values.

2. To determine the time of response in cSCC TILs. This will be measured from the time from the first visit until objective tumor response (CR or PR) is identified.

3. To measure the duration of overall response (DOR) of TILs. This will be measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or progressive disease (PD) is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started. If no recurrence or PD is documented after PR or CR is observed the time measurement will be performed at Visit 8.

4. To measure the durable response rate (DRR) of TILs. The duration of overall response is ORR lasting continuously for > than or equal to 6 months.

5. To measure the time to progression (TTP) of TILs. This will be measured from the time treatment is initiated until the first date that recurrence or progressive disease (PD) is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

6. To measure the overall response rate (CR+PR) of TILs by high frequency ultrasound and correlate it with clinical overall response rate.

7. Overall clinical response rate (CR+PR) of individual TILs injected with talimogene laherparepvec (not as overall subject response).

8. To determine the overall clinical response rate (CR+PR) observed in TNILs that are present in the treated anatomical location (if applicable).

3.3 Exploratory Objective

To determine the frequency of non-melanoma skin cancers 24 months prior to TVEC injections (or Visit 1), and then 12 months prior to the TVEC injections (or Visit 1), as compared to the frequency of non-melanoma skin cancers 12 months after the TVEC injections (or Visit 4) and then 24 months after the last injection (or Visit 4) if available.

4.0 BACKGROUND AND RATIONALE

4.1 Disease/Condition

Squamous cell skin cancer is the second most common cutaneous malignancy with estimated 700,000 cases of cutaneous SCC diagnosed each year in the US (2, 3). Based on certain characteristics, SCC of skin is classified into low-risk and high-risk disease. The features of low-risk disease are noted below (Table 2). According to Brigham and Women's Hospital, a low risk cSCC has fewer than two high risk features (Table 3) (1). High-risk features include a diameter of at least two centimeters, poorly differentiated histology, tumor invasion beyond subcutaneous fat and perineural invasion of nerve(s) greater or less than 0.1 mm in depth(1). Surgery (Moh's procedure) is the primary modality of treatment for cSCC of the head and neck with standard surgical resection recommended for SCC of other sites. Surgical excision has local failure rates of up to 15% (4).

Despite reasonable response rates, surgical excision can be challenging in patients with multiple synchronous lesions, or with a recent lesion history of multiple cSCCs. In addition, surgical excision of lesions in certain locations, such as lower extremities, can result in poor wound healing, infections and long-term complications (5). Local therapies such as cryosurgery, electro-desiccation and curettage, topical therapies (imiquimod or 5- fluorouracil), and photodynamic therapy, as well radiation therapy are other treatment options in low-risk SCC. According to the National Comprehensive Cancer Network, radiation therapy is the standard-of-care treatment for low risk cSCC for non-surgical candidates; however, it is recommended for patients older than 60 years because of

concerns of long-term sequelae (6). Adjuvant radiation and/or chemotherapy is used in patients with high-risk / advanced SCC as neo-adjuvant treatment, or adjuvant therapy to minimize the risk of local and distant recurrence.

Table 2: Low- Risk features of cutaneous SCC (7)
• Size <20 mm on trunk or extremities (excluding pre-tibia, hands, feet, nail units, and ankles) or <10mm in “mask areas” of face or <6mm in cheeks, forehead, scalp, and neck.
• Well - defined borders
• Primary tumors
• No immunosuppression
• Not a site of previous radiation therapy or chronic inflammation
• Slow growing tumor
• Absence of neurologic symptoms
• Well or moderately differentiated tumor
• Non adenoid (acantholytic), adenosquamous, or desmoplastic subtypes
• Depth less than 2 mm or Clark level IV or V, • No perineural or vascular involvement

Summary of American Joint Committee on Cancer (AJCC) and Brigham and Women’s Hospital (BWH)

AJCC	
T1	Tumor ≤ 2 cm in greatest dimension, with < 2 high-risk factors
T2	Tumor > 2 cm in greatest dimension, with ≥ 2 high-risk factors
T3	Tumor with invasion of orbit, maxilla, mandible or temporal bones
T4	Tumor with invasion of other bones or direct perineural invasion of skull base
BWH	
T1	0 high-risk factors
T2	1 high-risk factors
T3	2-3 high-risk factors
T4	≥ 4 high-risk factors

Adapted from Karia et al. (1).

Immunotherapy in Cutaneous SCC

Immune-evasion is a well-known mechanism by which cancer cells proliferate and spread. Immune checkpoint inhibition unmasks negative feedback of the cancer cells on cytotoxic immune response and is a proven therapeutic approach in multiple cancers including melanoma. A compromised immune-surveillance plays an important role in the pathogenesis of cutaneous SCC (8). A clear increase in the incidence of cutaneous SCC is noted in patients with immune deficiency and iatrogenic immune-suppression (post-transplant setting). cSCC is the most common cancer identified in immunosuppressed population (9). This experience supports the innovative approach to implement TVEC in cSCC. Immune-therapy has a definite role in treatment of cutaneous SCC.

Imiquimod is a topical immune-modulator that works by binding to toll-like receptors 7 & 8, inducing a T-cell mediated cytokine response cascade and tumor cell destruction. Imiquimod is currently approved for use in anogenital warts, actinic keratoses, and superficial basal cell carcinomas. It has been proven to be effective in squamous cell carcinoma in situ (10). Interferon is another immunomodulator currently used in treatment of multiple hematological malignancies and melanoma. In a European study, 52 patients with cSCC were treated with intralesional interferon, complete response was observed in 59.6% of patients. On long-term follow up, ranging more 5 to 10 years, recurrence was observed in only 2 of the 52 patients treated with interferon, demonstrating that immune-modulation can be an effective treatment strategy in cutaneous SCC (11). The primary rationale for this protocol is based on the known effectiveness of immunological targeted therapies in cSCC such as PD-1/PD 1 inhibition, imiquimod, and interferon.(12-16).

Talimogene laherparepvec is an oncolytic immunological agent derived from herpes simplex virus type-1. It is genetically modified and engineered to replicate within tumors. It works by several mechanisms including direct destruction of cancer cells, production of GM-CSF to enhance systemic antitumor immune recognition and destruction of cancer cells. In the phase 3 trial that led to FDA approval of talimogene laherparepvec in unresectable IIIB to IV staged melanoma, 436 patients were randomly assigned to talimogene laherparepvec or GM-CSF. The study showed an improvement of durable response rates (16.3% vs. 2.3%, $p<0.001$) and overall response rate (26.4% vs. 5.7%, $p<0.001$) (ORR) (17).

There is limited experience implementing TVEC in cSCC. One study identified effectiveness of oncolytic viruses in experiential SCC murine models with demonstration of systemic immunity (18). Other studies have also shown that the implementation of oncolytic viruses as a therapeutic approach for the treatment of cSCC—with HSV (19, 20) and with Adenovirus (21-23).

We hypothesize that talimogene laherparepvec can be an effective minimally invasive immune- therapy in low-risk, unresectable cSCC. Also, injection of talimogene laherparepvec in a SCC lesion can elicit a systemic anti-tumor response, resulting in a

therapeutic response beyond the location where the primary lesion is being treated.

Nonclinical evaluation has also confirmed that GM-CSF enhances the immune response generated, enhancing both injected and uninjected tumor responses. As of the 23 February 2018 data cutoff date for this investigator's brochure, 15 clinical studies (including two extension studies) have been or are being conducted in several advanced tumor types (advanced solid tumors, melanoma, squamous cell cancer of the head and neck [SCCHN], and pancreatic cancer). Ten studies were conducted in the setting of metastatic melanoma; eight of these studies employ(ed) talimogene laherparepvec as monotherapy and the remaining two studies employ talimogene laherparepvec in combination with either ipilimumab or pembrolizumab. As of the cutoff date, 893 subjects were treated with talimogene laherparepvec and have provided efficacy and/or safety data; 31 subjects from these studies entered the extension studies. A non-interventional registry study (20120139) is ongoing to investigate the long-term survival and safety of subjects previously treated with talimogene laherparepvec in prior clinical trials. In addition to the two expanded access protocols, one each in the United States (US) and European Union (EU), are also ongoing.

4.2 Investigational Product (24)

Talimogene laherparepvec (formerly known as OncoVEX GM-CSF) is an investigational, oncolytic immunotherapy based on a modified herpes simplex virus type-1 (HSV-1) that is designed to selectively replicate in tumor tissue and to stimulate a systemic antitumor immune response. In talimogene laherparepvec, the HSV-1 viral genes ICP34.5 (the "neurovirulence factor" that promotes viral replication in normal cells with an intact anti-viral response but is not required for replication in tumor tissue in which anti-viral responses are often defective) and ICP47 (which blocks antigen presentation by major histocompatibility complex molecules of infected cells) have been deleted. In addition, deletion of ICP47 leads to increased and earlier expression of US11 which enhances viral replication in infected tumor cells. The coding sequence for human granulocyte macrophage colony stimulating factor (GM-CSF) is inserted in place of ICP34.5, to enhance the immune response to tumor antigens released during oncolysis. Intralesional administration of talimogene laherparepvec results in oncolysis of cells within injected tumors. Iterative viral replication within permissive tumor tissue results in lytic cell destruction and local release of progeny virus as well as of tumor cell antigens. GM-CSF, the product of the viral transgene, is also produced locally to recruit and stimulate antigen presenting cells which, in addition to relevant tumor-derived antigens, are required for the initiation of a systemic antitumor immune response. Overall, this strategy is expected to result in the destruction of injected tumors via oncolysis and also uninjected sites of disease (including micro-metastases) via a systemic antitumor immune response, to curtail tumor progression and to reduce local and distant tumor recurrence.

In a clinical study in subjects with melanoma that included quantitative polymerase chain reaction (qPCR) testing of talimogene laherparepvec DNA in blood, urine, injection site, occlusive dressings, oral mucosa, anogenital area, and suspected

herpetic lesions, talimogene laherparepvec DNA was present in all sites during the study. Among subjects with detectable talimogene laherparepvec DNA in the blood, urine, oral mucosa, and anogenital area, no samples had detectable talimogene laherparepvec DNA 30 days after the end of treatment. For subjects with detectable DNA in injected lesions, no samples had detectable talimogene laherparepvec DNA 60 days after the end of treatment. Currently, there is no clinical data available for talimogene laherparepvec DNA detection in treatment sites for cSCC.

4.3 Preclinical Experience- Not applicable

The use of talimogene laherparepvec in the treatment of cSCCs has no preclinical data to report.

4.4 Clinical Experience-Not applicable

There is no clinical experience on the use of talimogene laherparepvec with cSCC.

5.0 INVESTIGATIONAL PRODUCT

5.1 Investigational Product

In accordance with the protocol the following will be referred to as investigational product (IP):

- Talimogene laherparepvec at nominal concentration of 10^6 plaque forming units (PFU)/mL with approximately 1.15 mL in a 2 cc vial for the initial dose

- Talimogene laherparepvec at nominal concentration of 10^8 PFU/mL with approximately 1.15 mL in a 2 cc vial for the second and subsequent doses

For each of the IP used, the preparation procedure(s) and storage condition(s) should comply with the instructions provided for each and every dose of the IP that is administered.

- Description of Investigational Product

Talimogene laherparepvec is an oncolytic immunotherapy based on herpes simplex virus type 1 (HSV-1) which is capable of generating an immune response specific to a subject's tumor. Talimogene laherparepvec induces viral lysis of tumor cells, followed by stimulation of a tumor-specific immune response.

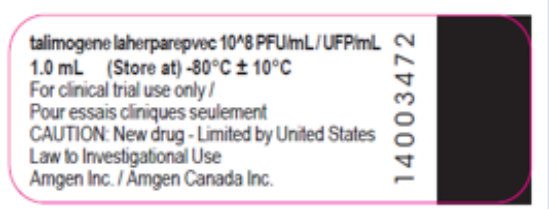
5.2 Investigational product supply

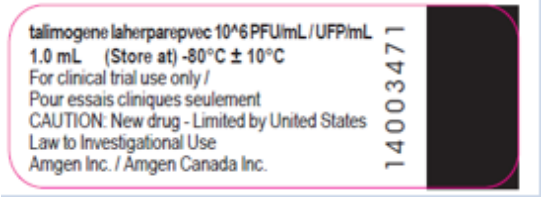
Talimogene laherparepvec will be presented as a sterile, semi-translucent to opaque suspension, practically free from particles, preservative free frozen liquid in a single-use 2.0cc Crystal Zenith Resin vial. Each vial will contain talimogene laherparepvec at a nominal concentration of 10^6 PFU/mL or 10^8 PFU/mL for intratumoral injection in a solution containing disodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride, sorbitol, myo-inositol and Water for Injection (WFI). Each 2cc vial will contain approximately 1.15 mL of talimogene laherparepvec. Vials are appropriately filled to ensure that a sufficient deliverable dose is provided. Each vial is intended for single use only.
Vials will be sealed with gray rubber stoppers, Fluorotec-coated on the product side. The vial caps will be color-coded and may be used to help distinguish between the 10^6 PFU/mL and 10^8 PFU/mL vial concentrations.

Information provided on the labels for talimogene laherparepvec will comply with ICH, GCP and local regulatory requirements.

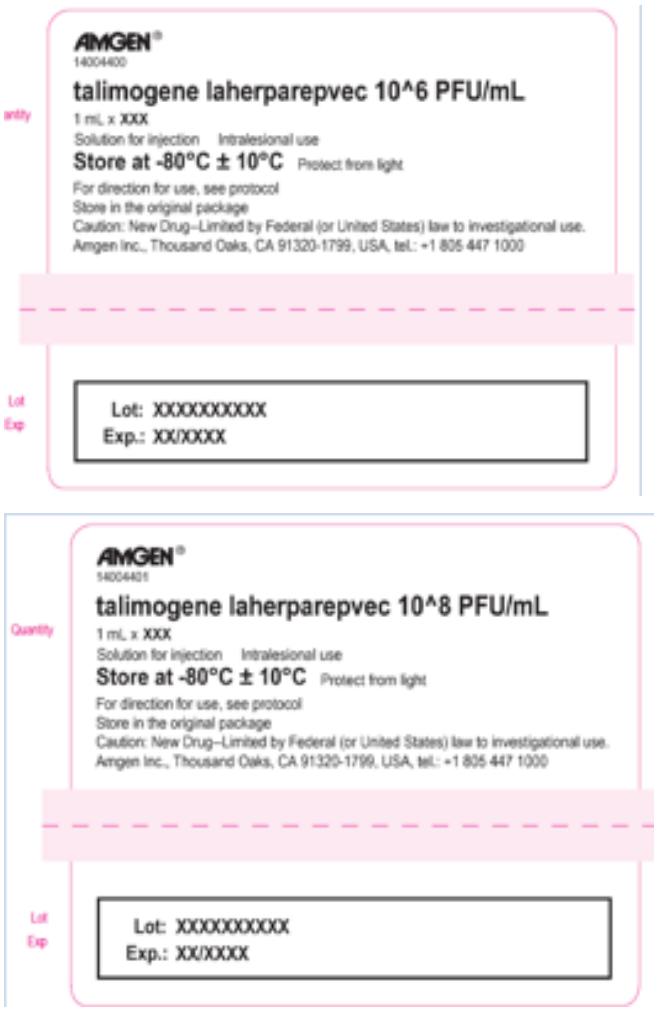
Examples of Product Labels (talimogene laherparepvec):

<u>Examples of Vial Labels (talimogene laherparepvec):</u>





<u>Examples of Box Labels (talimogene laherparepvec):</u>



5.3 Investigational Product Accountability

The Sponsor- investigator will take the following actions with regard to study drugs in concurrence with international regulatory requirements. All study medication will be delivered to the University of Arizona Cancer Center Research Pharmacy. The following items will be addressed with the Research Pharmacy Team.

1. Upon receipt of clinical study materials the Clinical Research Pharmacy or designated individual on the study team will check the details of the supplies and document receipt on invoice and drug accountability record (DAR).

2. The Pharmacy will keep study drugs in a locked and secure storage facility, accessible only to those individuals authorized by the investigator to dispense this study drug. All study drug will be stored separately from any other medications.

3. The Pharmacy or designee will maintain a temperature log to ensure that study drug is stored at manufacturer recommended room temperature at all times.

4. The Pharmacy or designated individual will maintain an inventory. This will include the description and quantity of study drug received during the course of this study, as well as a record of the materials that are dispensed and returned (how much, to whom, and when). This inventory record shall indicate the quantity and description of all study drugs on hand at any time during the course of the study.

5. At the conclusion or termination of this study, the Pharmacy and investigator agree to conduct a final drug supply inventory, to record the results of this inventory and all remaining study drug will be destroyed on site per institutional policies.

6. The investigator agrees not to supply study drug to any person except study personnel and subjects in this study.

5.4 Storage

Upon receipt, and to ensure stability of talimogene laherparepvec, vials must be stored under the conditions specified below.

Talimogene laherparepvec is shipped by air courier or truck transit maintained at -70°C or below in a qualified shipper suitable for biological substance shipments. Talimogene laherparepvec vials will arrive in a secondary packaging container and should be immediately (within 90 seconds) placed in a non-cycling freezer maintained at -70°C or below in a secured location until planned use. The set point for the freezer should be at -80°C. Frost-free, auto defrost freezers must **not** be used since they cycle to warmer temperatures several times a day.

Table 3 Acceptable Storage Temperature

Freezer Set Point (ºC)	Acceptable Parameters:	Acceptable Range:
-80°C	(+/- 10°C)	-70° to -90°C

Talimogene laherparepvec is stable if maintained in accordance with the guidelines described in this document and the provided expiration date.

5.5 Preparation of Talimogene Laherparepvec

The following steps should be followed for drug preparation:

For U.S. sites, the talimogene laherparepvec Safety Data Sheet categorizes the drug as a Bio Safety Level (BSL) 1, thus use of BSL 1 containment procedures is recommended. Unless otherwise directed by local regulations:

- The use of a microbiological safety cabinet or hood for the dispensing of talimogene laherparepvec or for dose preparation is not required.

- Talimogene laherparepvec may be safely drawn up into syringes in the room used for product administration, although this may also optionally occur elsewhere (e.g., in the pharmacy).
- Any side room away from other subjects can be used for talimogene laherparepvec administration, although local/regional guidelines should be followed.

Please follow local/regional guidelines where applicable.

Materials Inventory

- Sterile 18-26 gauge disposable needle(s) to withdraw talimogene laherparepvec from vials
- Appropriately sized sterile syringe(s), based on administration strategy in the protocol
- Laboratory coat, gloves and safety glasses
- Alcohol swabs

5.6 Handling

Thawing of Frozen Vials
To ensure proper usage of talimogene laherparepvec at the investigator site, please follow the instructions below:

- All personnel handling the talimogene laherparepvec or material contaminated with talimogene laherparepvec must observe safety precautions (e.g., wear a laboratory coat, safety glasses and gloves), as per local or BSL classification guidelines.

- Determine which box labeled with the appropriate concentration, 10^6 PFU/mL or 10^8 PFU/mL, is to be prepared
- Remove the number of frozen vials from the box that have been calculated for administration and immediately (within 1 minute) return the remaining vials to the freezer. Care should be taken to avoid unintended thawing of vials that will not be used. The time the vials are removed from the freezer must be recorded.

- Thaw frozen vials until liquid at **room temperature (20°C to 25°C or 68°F to 77°F)**. Thaw should take approximately 30 minutes. Please ensure vial is protected from light during the thaw process.

Please Note: During the thaw process sites should adhere to local procedures to ensure the required temperature is maintained and monitored.

<u>During the thaw:</u>

- Leave vials undisturbed, except to gently swirl to check for completion of thaw.

- Never shake vials vigorously, especially during the thawing process.

After the thaw:

- Gently swirl the vial to ensure the contents are mixed to a homogeneous solution free of ice.
- Carefully check the vial for damage (e.g., cracks). Quarantine damaged vials and obtain further instructions for destruction and reporting.
- Refer to Table 4 below for clinical handling storage times.
- Discard materials used in the thawing (e.g., gloves) following appropriate local/regional or BSL classifications guidelines.

Preparation of Dosing Syringe for 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) as per local/regional or BSL classification guidelines.
- The prepared talimogene laherparepvec dosing syringe must be properly labeled in accordance with current ICH GCP and local/regional or BSL classification requirements prior to administration.
- Clean talimogene laherparepvec vial stopper with an alcohol swab.
- Withdraw appropriate volume of talimogene laherparepvec required with the appropriate number of sterile syringe(s) and 22-26 gauge needle(s). Cap each syringe as per local practice.
- Please refer to the Table 4 below for the Clinical Handling Timelines. Discard any prepared syringes not used for administration within the specific times stated.
- Discard materials used in the preparation (e.g., gloves, needles) in accordance with local/regional or BSL classification guidelines.

Table 4: Clinical Handling Timelines

General product handling considerations
Thaw • Thaw frozen talimogene laherparepvec vials at 20°C to 25°C (68°F to 77°F) until fully liquid (approx. 30 minutes at the stated temperature range). Do not expose vials to higher temperatures. • Swirl gently. Do not shake. • Do not refreeze thawed talimogene laherparepvec.

Storage and Preparation

- Store talimogene laherparepvec (in vial or syringe) protected from light at all times until administration.
- Due to the absence of a preservative in the formulation please minimize storage time in the syringe where possible.
- **Please note** that storage of 10^6 and 10^8 PFU/mL talimogene laherparepvec in the vial followed by in the syringe is permitted for the same storage condition only e.g. both vial and syringe stored in the refrigerator. When thawed 10^6 and 10^8 PFU/mL is stored in both vial and syringe, the storage time in syringe cannot exceed allowable syringe storage time **and** the cumulative vial and syringe storage time cannot exceed the total allowable storage time. See below for specific details on allowable durations for each container and temperature combination.

Administration

- If talimogene laherparepvec is not administered within the timeframes and not handled at the temperatures indicated, then it must be discarded.
- Reporting of temperature excursions during clinical administration is not required.

For 10^6 and 10^8 PFU/mL

Thaw requirement	***Storage of vial* from time of thaw completion**		***Storage of prepared syringe* from time of draw up from vial**	
20°C (68°F) to 25°C (77°F)	**9°C (48°F) to 27°C (80°F)**	**2°C (36°F) to 8°C (46°F)**	**9°C (48°F) to 27°C (80°F)**	**2°C (36°F) to 8°C (46°F)**
Thaw until fully liquid (approx. 30 minutes at this temperature range for both 10^6 and 10^8 PFU/mL)	**4 hours** for 10^6 PFU/mL[1]	**12 hours** for 10^6 PFU/mL[1]	**2 hours** for 10^6 PFU/mL[2]	**4 hours** for 10^6 PFU/mL[2]
	4 hours for 10^8 PFU/mL[1]	**48 hours** for 10^8 PFU/mL[1]	**4 hours** for 10^8 PFU/mL[2]	**8hours** for 10^8 PFU/mL[2]

[1]If vial is stored at ambient or refrigerated temperatures after thaw then the IP must be withdrawn from the vial and administered immediately. No syringe storage time is allowed after ambient or refrigerated storage in the vial has already occurred.
[2]Syringe must be prepared immediately after thaw is complete. Where multiple syringes are being prepared then all syringes must be prepared in the minimum necessary time and any delays in preparation must be avoided. No thawed vial storage time (outside of time required for preparation of syringes) is allowed if syringe storage time is needed.

6.0 SUBJECT ELIGIBILITY

Investigators will maintain an electronic subject log (in the UACC OnCore system) of all potential (i.e. consented) study subjects, which will include as applicable

(demographics, informed consent, eligibility, treatment assignment, on treatment, off treatment, follow up and off study dates).

6.1 Inclusion Criteria

a. Able to give informed consent in English or Spanish
b. Age ≥ 18
c. Have at least one >0.5 cm to <5.0 cm, histologically confirmed low risk cutaneous SCC (including kerathoacanthomas)
- Size >0.5 cm on trunk or extremities (excluding face, neck feet, nail units, and ankles)
- Clinically consistent with primary tumors.
- Lesion considered unresectable (as defined in Section 1.2)
- Recurrent lesions will be considered eligible if additional inclusion criteria are met.
- No immunosuppression
- Not a site of previous radiation therapy or chronic significant inflammation
- Fast growing lesions (doubling in size over a 4 week period of time) will be included if they are clinically suggestive of cSCC of the keratoacanthoma type.
- Well or moderately differentiated tumor as confirmed by skin biopsy
- Depth less than 2 mm (for non KA type cSCC)
- No perineural or vascular involvement in preliminary biopsy.

d. Partial biopsy of squamous cell skin cancer identified as a target lesion(s) to determine the histological differentiation of the tumor or other adverse histological features
e. In patients with multiple lesions, up to 3 lesions in a similar anatomical site, (trunk, limbs etc) that is at least 10 cm apart can be selected.
f. Maximum of 5 lesions per patient can be selected for treatment
g. Adequate organ function determined within 28 days prior to enrollment, defined as follows:
h. Hematology:
- Absolute neutrophil count ≥ 1500/mm3 (1.5x109/L)
- Platelet count ≥ 75,000/mm3 (7.5x109/L)
- Hemoglobin ≥ 8 g/dL (without need for hematopoietic growth factor or transfusion support)

i. Renal
- 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 within normal limits. Creatinine clearance should be determined per institutional standard)

j. Hepatic
- Serum bilirubin ≤ 1.5 x ULN
- Aspartate aminotransferase (AST) ≤ 2.5 x ULN

- Alanine aminotransferase (ALT) ≤ 2.5 x ULN

k. Coagulation

- International normalization ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN, unless the subject is receiving anticoagulant therapy, in which case PT and partial thromboplastin time (PTT)/ activated PTT (aPTT) must be within therapeutic range of intended use of anticoagulants.
- PTT or aPTT ≤ 1.5 x ULN unless the subject is receiving anticoagulant therapy as long as PT and PTT/aPTT is within therapeutic range of intended use of anticoagulants.

l. Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to enrollment. If urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

6.2 Exclusion Criteria*:*

a) Any patient with diagnosis of invasive cancer in the last 3 years with the exception of stage I and II melanoma, cutaneous BCC and SCCs will be excluded.

b) Subjects on acitretin, capecitabine, topical chemotherapies or treatments. If participants have been on acitretin or capecitabine for up to 10 days, then no wash out period is required. If they have been on for more than 10 days, then they are required to do a wash out period of 30 days.

c) Subjects on topical skin cancer directed therapies (fluorouracil, levulan-with photodynamic therapy, imiquimod, diclofenac, ingenol mebutate) will require a 30 days wash out window if applied withing the same anatiomic location. If applied at other anatomical sites a 10 days wash out period will be required.

d) History or evidence of symptomatic autoimmune disease (eg, pneumonitis, glomerulonephritis, vasculitis, or other), or history of active autoimmune disease that has required systemic treatment (ie, use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in past 2 months prior to enrollment. 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.

e) Evidence of clinically significant immunosuppression such as the following:

- Primary immunodeficiency state such as Severe Combined Immuno deficiency Disease
- Acquired immunodeficiency syndrome
- Concurrent opportunistic infection
- Receiving systemic immunosuppressive therapy (> 2 weeks) including oral steroid doses > 10 mg/day of prednisone or equivalent within 2 months prior to enrollment.

f) Active herpetic skin lesions or prior complications of herpetic infection (e.g., herpetic keratitis or encephalitis).

g) Requires intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (e.g., acyclovir), other than intermittent topical use.

h) Previous treatment with talimogene laherparepvec or any other oncolytic virus

i) Prior therapy with tumor vaccine

j) Received live vaccine within 28 days prior to enrollment.

k) Currently receiving treatment with another investigational device or drug study, or < 28 days since ending treatment with another investigational device or drug study(s)

l) Other investigational procedures while participating in this study are excluded.

m) Known to have acute or chronic active hepatitis B infection

n) Known to have acute or chronic active hepatitis C infection

o) History of other malignancy within the past 3 years with the following exceptions:

- adequately treated mucosa associated lymphoid tissue (MALT) tumor
- malignancy treated with curative intent and with no known active disease present for ≥ 3 years before enrollment and felt to be at low risk for recurrence by the treating provider
- adequately treated non-melanoma skin cancer, lentigo maligna, stage I or II cutaneous melanoma, without evidence of disease.
- adequately treated cervical carcinoma in situ without evidence of disease
- adequately treated breast ductal carcinoma in situ without evidence of disease
- prostatic intraepithelial neoplasia without evidence of prostate cancer
- adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ

p) Subject has known sensitivity to talimogene laherparepvec or any of its components to be administered during dosing.

q) Female subject is pregnant or breast-feeding, or planning to become pregnant during study treatment and through 3 months after the last dose of talimogene laherparepvec

r) 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. (Note: Women not of childbearing potential are defined as: Any female who is post-menopausal [age ≥ 55 years with cessation of menses for 12 or more months or less than 55 years but not spontaneous menses for at least 2 years or less than 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).

s) Sexually active subjects and their partners unwilling to use male latex condom to avoid potential viral transmission during sexual contact while on treatment and within 30 days after treatment with talimogene laherparepvec.

t) Subject who is 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 children under the age of 1 year, during talimogene laherparepvec treatment and through 30 days after the last dose of talimogene laherparepvec.

6.3 Enrollment

All subjects who complete the screening period of the study will be enrolled and assigned a unique sequential subject identification number. This number will be used to identify the subject throughout the clinical study and will be used on all applicable study documentation related to that subject. The subject identification number will remain constant throughout the study.

The written informed consent document(s) must be signed and personally dated by the subject or by the subject's legally authorized representative and completed to a fully executed informed consent document and processed per the institution standard operating procedures.

Before subjects may be entered into the study, a copy of the written institutional review board (IRB) approval of the protocol, informed consent form (ICF), and all other applicable subject information and/or recruitment material must be on file at the institution.

7.0 STUDY PLAN

7.1 IP/treatment regimen

The recommended volume of talimogene laherparepvec to be injected into the tumor(s) is dependent on the size of the tumor(s) and should be determined according to the injection volume guideline in Table 5. The maximum dose to be given is 4.0 ml per injection visit.

Table 5: 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
> 0.1 to 0.5 cm	0.1 mL

7.2 Pre-medications

There are no medications that need to be taken before the injections however the patient will be given the choice to take Ibuprofen or acetaminophen prior to the injections.

7.3 Rescue Medications – Not applicable

7.4 Excluded medications/treatments

The following medications and treatment are excluded during the entire study participation including follow up visits.

- Oral medications: Acitretin, xeloda, vismodegib, and niacin/nicotinamide (see wash out periods for certain medications).
- Topical medications at the anatomical study site: fluorouracil, levulan (with photodynamic therapy), imiquimod, diclofenac, ingenol mebutate.
- Injectable medications: Fluorouracil (Adrucil) on the anatomical area of the targeted cSCC) during active participation in the study.

Subjects can re-initiate systemic intervention once Visit 8 is completed.

8.0 REQUIREMENTS FOR TREATMENT

8.1 Standard dose use

The standard dose for the study will be according to the dosing chart listed as Table 4 under 7.1. The maximum total dose will be 4mL per injection visit.

8.2 Dose reductions

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 (defined in dosing section) 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.

8.3 IP treatment delays

If an unexpected DLT occurs, talimogene laherparepvec administration should be delayed until the DLT has resolved to at least CTCAE version 4.0 Grade 1. If talimogene laherparepvec dosing is delayed by more than 6 weeks from the date of the planned dose due to the occurrence of an adverse event that is considered related to talimogene laherparepvec, the subject should be permanently taken off talimogene laherparepvec treatment.

8.4 Adverse Drug Reactions (ADRs)

Important Identified Risks

Important Identified Risks with talimogene laherparepvec treatment are listed below.

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

- Disseminated herpetic infection including serious cases of disseminated herpetic infection, have been reported in patients treated with talimogene laherparepvec.
- Accidental exposure of healthcare providers (HCP) to talimogene laherparepvec.
- Immune-mediated adverse reactions

Important Potential Risk

Important Potential Risks with talimogene laherparepvec treatment are listed below.

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

- Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation).
- Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients.
- Talimogene laherparepvec-mediated anti-GM-CSF antibody response.

Adverse drug reactions observed in talimogene laherparepvec clinical trials are listed below in Table 6. Consult the current Investigator's Brochure for the full information on ADRs.

Table 6. ADRs Observed in Talimogene Laherparepvec Clinical Trials

System Organ Class Preferred Term	**CIOMS Frequency** **(Very Common: ≥10% Common: 1%-<10% Uncommon: <1%)**
General disorders and administration site conditions	
Fatigue	Very Common
Chills	Very Common
Pyrexia	Very Common
Influenza like illness	Very Common
Malaise	Common
Axillary pain	Common
Injection site reactions*	Very Common
Gastrointestinal disorders	
Nausea	Very Common
Vomiting	Very Common
Diarrhea	Very Common
Constipation	Very Common
Abdominal pain	Common
Abdominal discomfort	Common
Musculoskeletal and connective tissue disorders	
Myalgia	Very Common
Arthralgia	Very Common
Pain in extremity	Very Common
Groin pain	Common
Skin and subcutaneous tissue disorders	
Vitiligo	Common
Rash	Common
Dermatitis	Common
Infections and infestations	
Cellulitis	Common
Oral herpes	Common
Incision site infection	Uncommon
Nervous system disorders	
Headache	Very Common
Dizziness	Common
Eye disorders	
Herpetic keratitis	Uncommon

System Organ Class Preferred Term	CIOMS Frequency (Very Common: ≥10% Common: 1%-<10% Uncommon: <1%)
Respiratory, thoracic and mediastinal disorders	
Oropharyngeal pain	Common
Obstructive airway disorder	Uncommon
Metabolism and nutrition disorders	
Dehydration	Common
Injury, poisoning and procedural complications	
Contusion	Common
Procedural pain	Common
Wound complication	Common
Wound secretion	Common
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Tumour pain	Common
Infected neoplasm	Common
Plasmacytoma at the injection site	Uncommon
Investigations	
Weight decreased	Common
Vascular disorders	
Deep vein thrombosis	Common
Flushing	Common
Blood and lymphatic system disorders	
Anemia	Common
Immune system disorders	
Worsening psoriasis	Uncommon
Pneumonitis	Uncommon
Glomerulonephritis	Uncommon
Vasculitis	Uncommon
* Injection site reactions include: very common term of injection site pain, common terms of injection site erythema, injection site hemorrhage, injection site swelling, injection site reaction, injection site inflammation, secretion discharge, injection site discharge, uncommon term of injection site warmth.	

Treatment of ADRs

Subjects will receive medical treatment if injured as a result of study participation. The principal investigator and staff will help the participant get medical care for associated adverse events. The subject or the subject's insurance will be charged for that treatment. The study will not provide monetary compensation for medical treatment. Subjects do not lose legal rights to seek payment by signing the consent form. All reported ADRs will be documented according to safety monitoring and reporting standards (See Section 11 and 12).

8.5 Definition of a Dose Limiting Toxicity (DLT)

Definitions of dose-limiting toxicity:

Toxicity will be evaluated according to CTCAE version 4.0. DLT will be defined as any of the following talimogene laherparepvec-related toxicity during treatment and up to 30 days after end of treatment.

The following herpetic events should be considered as DLTs:

- Serious herpetic events such as herpetic encephalitis, encephalomyelitis or disseminated herpetic infection.
- Any herpetic events (with the exclusion of oral and genital outbreaks) that are at least possibly due to talimogene laherparepvec and require 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 anti-viral treatment is required, talimogene laherparepvec treatment should be permanently discontinued.

Consider also including the following as DLTs:

- 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:
    - medical intervention is required, or
    - the abnormality leads to hospitalization, or
    - the abnormality 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 bleeding event requiring intervention.
- Any other intolerable toxicity leading to permanent discontinuation of talimogene laherparepvec.
- Grade 5 toxicity (ie. death).

9.0 STUDY PROCEDURES

9.1 Screening- Visit 0

Potential subjects will enter the screening period of the study after a completely executed informed consent has been obtained.

- Review of inclusion/exclusion criteria
- Medical and medication history and dermatological history review
- Skin check by the study provider
- Urine pregnancy test (72 hours before enrollment)
- Screening blood work to include a complete blood count (CBC), comprehensive metabolic panel (CMP) and pregnancy test (hCG) if urine pregnancy test comes back positive or inconclusive
- Identification of the target lesions for the study. One subject can have up to 5 TILs. One to three TILs may be on the same anatomical area but will need to be 10 cm apart. Up to 10 TNILs can be followed with no more than 2 TNILs selected in the same anatomical area as a TIL.
- Photographing and measuring of the target lesions
- Biopsy of any suspected non-target skin cancers (ie BCC). If a non-SCC skin cancer is confirmed the corresponding treatment should be completed prior to initiation of study intervention.
- Partial biopsy of lesions suspicious for cSCC (both TILs and TNILs) that have not already been biopsied. A partial shave or small punch biopsy may be done to sample the tissue.
- Vital signs obtained to include blood pressure, pulse, temperature, height and weight
- Ultrasound of TILs at Radiology Department for baseline evaluation (Appendix B)
- Assign screening number starting with the 2-digit site number followed by SCC

and a 3-digit sequential number, starting with -001 and increasing by one for each subject. If a subject fails the screening visit they may be replaced by an additional subject.

9.2 Enrollment- Visit 1

- See 9.3 for enrollment visit details

9.3 On IP treatment

Registered subjects will be treated with talimogene laherparepvec based on lesion size, administered at of 10^6 (1 million) PFU/mL administered intralesionally for the first visit and 10^8 (100 million) PFU/mL administered intralesionally for subsequent visits (V2-4). A full description of treatment plan and dosing is outlined in sections 2.4 and 7.1.

Visit 1- First injection visit (7 - 28 days +/- 3 days)

- Skin exam only of target lesions
- Review of all blood work and confirmation to continue in the study
- Review of the biopsies of SCC lesions to confirm SCC diagnosis
- Assess adverse events
- Assess con med changes
- Complete inclusion/exclusion criteria
- Assign subject study number starting with SCC-01 and continue to be assigned sequentially
- Vital signs
- Photograph and measure all target lesions (Appendix A)
- Inject TILs
- Provide patient education on any side effects to expect and the treatment of the injected sites
- Schedule the next injection visit in 3 weeks

Visit 2- Second injection visit (21 days +/- 3 days)

- Vital signs
- Review con meds
- Assess for any adverse events
- Skin exam only of target lesions
- Photograph and measure all target lesions (Appendix A)
- Inject TILs
- Provide patient education on any side effects to expect and the treatment of the injected sites
- Schedule the next injection visit in 2 weeks

Visit 3- Third injection visit (14 +/- 3 days)

- Vital signs
- Review con meds

- Assess for any adverse events
- Skin exam only of target lesions
- Photograph and measure all target lesions (Appendix A)
- Inject TILs
- Provide patient education on any side effects to expect and the treatment of the injected sites
- Complete bloodwork (CBC, CMP)
- Schedule the next injection visit in 2 weeks.

Visit 4- Fourth injection visit (14 +/- 3 days)
- Vital signs
- Review con meds
- Assess for any adverse events
- Skin exam only of target lesions
- Photograph and measure all target lesions (Appendix A)
- Inject TILs
- Provide patient education on any side effects to expect and the treatment of the injected sites
- Schedule the first follow up visit in 4 weeks.

Visit 5- First follow up visit (28 +/- 7 days)
- Vital signs
- Review con meds
- Assess for any adverse events
- Skin exam only of target lesions
- Photograph and measure all target lesions (Appendix A)
- Schedule the second follow up visit in 4 weeks

Visit 6- Second follow up visit (28 +/- 7 days)
- Vital signs
- Review con meds
- Assess for any adverse events
- Skin exam only of target lesions
- Photograph and measure all target lesions (Appendix A)
- Ultrasound of TILs at Radiology Department for follow-up evaluation(Appendix B)
- Schedule the third follow up visit in 6 weeks

Visit 7- Third follow up visit (42 +/- 10 days)
- Vital signs
- Review con meds
- Assess for any adverse events
- Skin exam only of target lesions
- Photograph and measure all target lesions (Appendix A)
- Schedule the next follow up visit in 14 weeks.

Visit 8 - Fourth follow up visit (98 +/- 21 days)

- Vital signs
- Review con meds
- Assess for any adverse events
- Skin exam only of target lesions
- Photograph and measure all target lesions (Appendix A)

Visit 9 – Telephone Follow up (356 +/- 31 days) after Visit 1
- Assess for changes of target lesions
- If active lesion(s) are noted by the participant, they will follow up with a dermatologist and their records will be requested

9.4 Study Assessments

9.4.1 Tumor Measurements:

Tumor measurements will be done at each visit. Imaging assessment with high frequency ultrasound will be done at baseline and at the second follow-up visit (Visit 6). At baseline, up to 5 TILs that are at least 10cm apart will be selected to be followed over the course of the study. Up to 10 TNILs can be followed with no more than 2 TNILs selected in the same anatomical area as a TIL. Responses in TILs and TNILs will be measured serially. Clinical measurements will be performed with a millimeter measuring tape (Appendix A). All measurements will be selected that will be able to be followed clinically and for ultrasound evaluations. The RECIST 1.1 (Appendix B) response criteria will be used to evaluate tumor response. Individual tumor measurements will also be conducted to determine clinical management of TILs and TNILs. The timeframe for the clinical (primary endpoint) and evaluation will be at Visit 6 and for high-frequency ultrasound (secondary endpoints) at Visit 6 as well.

9.4.1.1 Tumor Response

Complete Response (CR): Complete disappearance of all TILs (whether measurable or not, and no new lesions at the site of injection) confirmed by an assessment 8 weeks after the end of the injections (Visit 6).

Partial Response (PR): Decrease in tumor burden ≥ 30% relative to baseline confirmed by an assessment 8 weeks after the end of the injections (Visit 6).

Duration of Overall Response (DOR): DOR is when the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or progressive disease (PD) is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started. If no recurrence or PD is documented after PR or CR is observed the time measurement will be performed at Visit 6 for PR and Visit 8 for CR.

Durable Response Rate (DRR): Measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) with the response lasting continuously for > than or equal to 6 months. For PD, the reference will be the

smallest measurements recorded since the treatment started.

Time to progression (TTP): This will be measured from the time treatment is initiated until the first date that recurrence or progressive disease (PD) is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Progressive Disease (PD): Progression is defined as >20% increase of at least 5 mm in the sum of the longest diameters of the target lesions or increase in tumor burden ≥ 20% relative to nadir (minimum recorded tumor burden) or the appearance of one or more new lesions confirmed by an assessment 8 weeks after the end of the injections (Visit 6).

- **Rapid PD (RPD):** Is defined as an increase of >50% in tumor burden for lesions >2 cm in diameter or 100% tumor burden increase for lesion ≤2cm between visits.

Stable Disease (SD): Not meeting criteria for CR or PR, in absence of PD (Decrease of tumor size <30% to increase in size <20% of less than 5 mm in the sum of the longest diameters of the target lesions).

9.4.1.2 Clinical Management of TILs and TNILs

Along with assessing the overall tumor response (see Section 9.4.1.1, Tumor Response), each individual lesion will be assessed to determine appropriate clinical management. The RECIST 1.1 (Appendix B) response criteria will also be used to evaluate each individual tumor response.

Individual Lesion Complete Response (IL-CR): Complete disappearance of target lesion (whether measurable or not, and no new lesion(s) at the site of the target lesion) confirmation by an assessment 8 weeks after the end of the injections (Visit 6).

Individual Lesion Partial Response (IL-PR): Decrease in tumor burden ≥ 30% relative to baseline confirmed by an assessment 8 weeks after the end of the injections (Visit 6).

Individual Lesion Progressive Disease (IL-PD): Progression is defined as >20% increase of at least 5 mm in the sum of the longest diameters of the target lesions or increase in tumor burden ≥ 20% relative to nadir (minimum recorded tumor burden) or the appearance of one or more new lesions confirmed by an assessment 8 weeks after the end of the injections (Visit 6).

- **Individual Lesion Rapid PD (IL-RPD):** Is defined as an increase of >50% in tumor burden for lesions >2 cm in diameter or 100% tumor burden increase for lesion ≤2cm between visits.

Individual Lesion Stable Disease (IL-SD): Not meeting criteria for CR or PR, in

absence of PD (Decrease of tumor size <30% to increase in size <20% of less than 5 mm in the sum of the longest diameters of the target lesions).

Table 7. Management of individual TILs and TNILs

	Individual Lesion Complete Response (IL-CR)	**Individual Lesion Partial Response (IL-PR)**	**Progressive Disease (PD)**	**Stable Disease (SD)**
TILs	• IL-CR to be determined at the latest by Visit 6 (8 week follow up), and will be followed for 6 months • No additional injections will be given to TILs who have achieved IL-CR prior to the 4th injection visit • If recurrent at any point after IL-CR has been documented, then alternative therapeutic intervention offered (surgical excision, radiation, intralesional therapy etc.) based on patient preference	• IL-PR will be followed and assessed at Visit 6 (8 week follow up) • If IL-SD is documented at Visit 6 or beyond, alternative therapeutic intervention will be offered • If IL-PR continues, TIL will be closely followed until Visit 8, where alternative therapeutic intervention will then be offered	• If IL-PD confirmed in two consecutive visits OR at Visit 6 (8 week follow up), TIL will be withdrawn and alternative therapeutic intervention given ○ If subject has additional TILs, will continue study participation ○ If subject has only one, subject will be withdrawn • If IL-RPD occurs, treatment will be deferred that visit and will be reevaluated next visit. ○ If IL-PD confirmed, lesion withdrawn from study and alternative therapeutic intervention ○ If subject has more than one TIL, then lesions will continue to be a part of the study	• IL-SD will be followed and assessed up to Visit 6 (8 week follow up) • Alternative therapeutic intervention will be offered if no IL-CR or IL-PR is observed by Visit 6.
TNILs	• IL-CR to be determined at the latest by Visit 6 (8 week follow up), and will be followed for 6 months • If recurrent at any	• IL-PR will be followed and assessed up to Visit 6 (8 week follow up) • Alternative therapeutic	• IL-PD at Visit 3 will undergo alternative therapeutic intervention	• IL-SD will be followed and assessed up to Visit 6 (8 week follow up) • Alternative therapeutic

	point after IL-CR has been documented at Visit 6, then alternative therapeutic intervention offered	intervention will be offered if no IL-CR is observed by Visit 6		intervention will be offered if no IL-CR is observed by Visit 6

9.4.2 High Resolution Ultrasonography of Squamous Cell Cancer:

The subjects will complete ultrasound assessments of their lesions at screening Visit (0), and at Visit 6 (second follow up visit).

METHOD:
Focused high frequency ultrasound of the skin lesion will be performed in department of medical imaging using clinical ultrasound equipment LOGIQ E9 (GE Healthcare, Milwaukee, WI) and S-3000 (Acuson; Siemens Medical Solutions, Mountain View, CA). Linear array transducers with upper frequencies of 8-18 MHz and 6-18 (5-14) MHz respectively utilized to obtain sonograms. Imaging will be performed using either custom made gel standoff pad or copious amount of cold ultrasound gel acting as standoff, especially in body parts where gel pad could potentially cause image degradation due to poor apposition. Scanning will be done gently without compression to avoid distortion of superficial lesions. Two-dimensional B-mode images will be acquired following transverse and longitudinal sweeps from right to left and from top to bottom. The ultrasound probe will be oriented along the longest dimension of the lesion to obtain sagittal and transverse measurements of the cancer. Calculations of lesion depth will be made at the deepest extension of the mass in either plane. Duplex Doppler will be used to evaluate tumor vascularity; spectral wave pattern and Doppler measurements will also be obtained.
The subjects will receive ultrasound assessments of their TILs at screening visit (0), and at visit 6 (first follow up visit).

IMAGE INTERPRETATION:
Normal anatomy: The three layers of skin, epidermis (thickness 0.06-0.6 mm), dermis (thickness 1-4 mm) and hypodermis (subcutaneous tissues; thickness 5-20 mm) can be visualized on high frequency ultrasound. The epidermis appears as the most superficial, well defined, hyperechoic, linear band producing the “entry echo” between the ultrasound gel and skin, which can be called as epidermal entry echo (EEE). Dermal layer below the epidermis is also hyperechoic, usually less echogenic than epidermis with hair follicles, vessels, and sebaceous glands appearing as hypoechoic areas within it. The hypodermis or subcutaneous tissue layer is hypoechoic with intervening hyperechoic connective tissue septa separating fat lobules. Underneath the skin, superficial fascia covering muscle may be identified linear hyperechoic structure (1, 2). Squamous cell carcinoma (SCC) is the second most common cancer of the skin after basal cell cancer which has a major tendency for local relapse and regional nodal involvement. Tumor infiltrates into the surrounding soft tissues, cartilage and bone. Sonographic appearance of SCC reveals inhomogeneous hypoechoic lesion with

marginal irregularities; Doppler may show the presence of low-resistance pulsatile flow signals within or at the periphery of the tumor. However, it could be challenging to image the cancer in presence of hyperkeratotic epidermis which leads to reflection and attenuation of the ultrasound waves.

Following treatment anticipatory Sonographic changes in the lesion are expected with loss of inhomogeneous hypoechogenecity and reduced Doppler flow. The cancer may become progressively isoechoic with loss of conspicuity.

9.4.3 Chart Review: Frequency of Nonmelanoma Skin Cancers (NMSCs)

Participants' charts will be reviewed to assess the number of nonmelanoma skin cancers before and after the intervention. The frequency of NMSCs before the intervention will include the 12 months before Visit 1 and the 24 months before Visit 1 if available. The frequency of NMSCs after the intervention will include the 12 months after the last injection visit (or Visit 4) and then 24 months after the last injection (or Visit 4) if available. This exploratory objective is an effort to quantify the abscopal effect those participants may experience.

9.5 End of IP treatment

Subjects that complete the planned treatment portion of the study will have move into the follow up period.

9.5.1 Follow up

Visit 5- First follow up visit (28 +/- 7 days)
- Vital signs
- Review con meds
- Assess for any Adverse Events
- Skin exam limited to all target lesions
- Photograph and measure target lesions (Appendix A)
- Schedule the next follow up visit in 4 weeks.

Visit 6- Second follow up visit (28 +/- 7 days)
- Vital signs
- Review con meds
- Assess for any Adverse Events
- Skin exam limited to all target lesions
- Photograph and measure target lesions (Appendix A)
- Schedule second ultrasound to be completed on TILs before next follow up visit
- Schedule the next follow up visit in 6 weeks.

Visit 7- Third follow up visit (42 +/- 10 days)
- Vital signs
- Review concurrent meds

- Assess for any Adverse Events
- Skin exam limited to all target lesions
- Photograph and measure target lesions (Appendix A)
- Schedule the next follow up visit in 14 weeks.

Visit 8 - Fourth follow up visit (98 +/- 21 days)
- Vital signs
- Review con meds
- Assess for any adverse events
- Skin exam limited to all target lesions
- If sites are free of disease, participant participation will be complete
- Photograph and measure target lesions (Appendix A)
- Complete subject payment form

Visit 9 – Telephone Follow up (356 +/- 31 days) after Visit 1

- Assess for changes of target lesions
- If active lesion(s) are noted by the participant, they will follow up with a dermatologist and their records will be requested

9.6 Early Treatment Termination

Subjects that terminate IP treatment prior to completing the planned treatment portion of the protocol will have an early termination visit within 30 days of ending the treatment portion of the study. Subjects will have a termination visit with the following procedures completed:

- Vital signs
- Review concurrent meds
- Assess for any Adverse Events
- Skin exam limited to all target lesions
- Photograph and measure Target lesions
- Complete bloodwork (CBC, CMP)
- Complete subject payment form

9.7 Offset Range (or Treatment Window)

The range of days when a treatment can be given.
- Visit 1 - 4: (+/-) 3 days
- Visit 5 - 6: (+/-) 7 days
- Visit 7: (+/-) 10 days
- Visit 8: (+/-) 21 days
- Visit 9: (+/-) 31 days

9.8 Off Study

Subjects will be considered off study when all planned treatment, early termination and follow-up visits have been completed, unless death or withdrawal of consent to continue participation occurs.

10.0 PHARMACOKINETIC STUDIES- Not for this study

10.1 Collection

10.2 Processing

10.3 Storage

10.4 Destruction

11.0 DATA AND SAFETY MONITORING PLAN

11.1 Identification of the DSMB obligated for oversight responsibilities

The University of Arizona Cancer Center Data Safety and Monitoring Board (DSMB) will provide ongoing oversight for this trial. This study has been assigned a high risk level by the DSMB.

11.2 Identification of the entity obligated for routine monitoring duties

Routine monitoring will be provided by the University of Arizona Cancer Center Quality Assurance/Quality Control (QA/QC) Program to ensure that the investigation is conducted according to protocol design and regulatory requirements.

This trial will also undergo real-time monitoring by the PI and study team, including documentation of real-time monitoring of any new or ongoing safety issues and regular meetings every month with the study team to review data and safety events. For individual participants, adverse events will be assessed every 4 weeks by the study coordinator according to the assessment schedule. A study-specific adverse event log will be reviewed and signed every four weeks by the PI. The PI will review all severe adverse events within 24 hours of reporting.

11.3 Monitoring progress and data review process

Routine monitoring of subject data will be conducted at least every month.
The first routine monitoring visit will include at a minimum:

- Informed consent – 100% of cases enrolled;
- Subject eligibility – 100% of cases, up to three subjects;

- Data review – 100% of cases, up to three subjects.

All subsequent monitoring visits will consist of randomly selected subject cases based on current enrollment and include continuing review of previously selected cases, as applicable.

A monitoring visit report and follow-up letter will be completed approximately two weeks after the routine monitoring visit; a copy will be maintained in the study file. A query/finding form or an electronic record will also be completed by the monitor to request additional source documentation, clarification, information or corrections to the OnCore CRF and/or regulatory records. The Clinical Research Coordinator or other applicable staff responsible for the study will be given a copy of this form, or will be notified of the electronic record for resolution of queries/findings. The query/finding form will be maintained with a copy of the visit report for follow-up at the next monitoring visit. Electronic records will be available in the institution database or provided by the QA/QC Program staff.

The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the OnCore Case Report Form (CRF), or other acceptable data formats. Source documentation supporting the study data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.

Case report forms, which include the inclusion/exclusion criteria form, adverse event forms and serious adverse event forms *[other forms, depending on study]* should be completed via the institution database or other acceptable data formats. All subject forms and study files will be stored in a secure area limited to authorized staff.

Note: Routine monitoring of regulatory documents and test article will be conducted every three months.

11.4 Process to implement study closure when significant risks or benefits are identified

The PI will be advised of all study related AEs and will determine if the study at a certain point may need to be closed due the AEs.

Study stopping criteria will include the following:

- Death within 30 days after the investigational treatment at least possibly related to the study treatment.
- Any herpetic event or complication requiring hospitalization that is at least possibly related to the investigational agent within 30 days to treatment.

Individual treatment stopping criteria will include the following:

- 75% or greater number of TILs meeting criteria for withdrawal.
- Identification of high-risk feature in one or more TILs during study participation.
- Persistent discomfort (consecutive weeks of lesion pain, burning, or itching of Grade 2 or more).

11.5 Description of adverse events and reporting procedures

ADVERSE EVENTS
An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Any and all adverse events will be recorded on the UMC adverse events record form and reviewed by the Principal Investigator.

All adverse events will be classified using either the MedDRA term or NCI Common Terminology Criteria for Adverse Events (CTCAE) 4.0 and will address:

- Grade
- Relationship to study drug (not related, unlikely, possible, probable, definitely)
- Causality other than study drug (disease related, concomitant medication related, intercurrent illness, other)
- Date of onset, date of resolution
- Frequency of event (single, intermittent, continuous)
- Event outcome (resolved, ongoing, death)
- Action taken (none, held, dose reduced, discontinued, medication given)

SERIOUS ADVERSE EVENTS
A serious adverse event (SAE) is any untoward medical occurrence that at any dose:
1) Results in death;
2) Is life-threatening;
3) Requires in-patient hospitalization or prolongation of an existing hospital stay;
4) Results in disability persistent or significant disability/incapacity, or:
5) Is a congenital anomaly/birth defect.

Note: A SAE may also be an important medical event, in the view of the investigator that requires medical or surgical intervention to prevent one of the outcomes listed above.

All serious adverse events, regardless of attribution, and any deaths will be reported within 24 hours of notification of the event to the sponsor and, if applicable, any collaborating entity. All serious adverse events and any deaths will be reported to the DSMB and to the University of Arizona Human Subjects Protection Program per the guidelines set forth in University of Arizona Cancer Center Data and Safety Monitoring Board Charter, Table 5: Adverse Event Reporting.

All serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and fully reviewed by the DSMB, every three months. The DSMB coordinator will review the SAE reporting process to confirm reporting requirements are met.

11.6 Plan for assuring data accuracy and protocol compliance

Routine study activity and safety information will be reported to the DSMB on a monthly basis, or more frequently if requested. These reports will include:

- Study activity, cumulative and for the period under review;
- Safety (narrative description on non-serious and serious adverse events, protocol pre-determined early stopping rules for safety or treatment-emergent adverse events);
- Predetermined protocol early stopping rules for efficacy/futility;
- Status of study in relationship to stopping rules;
- Current dose level of study agent;
- Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);
- Comments;
- Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies

Data, safety and study progress will be reported to:

- Human Subjects Protection Program (IRB) at least annually;
- Sponsor (if applicable) at least quarterly.

11.7 Identification of the sponsor or funding agency, as applicable

The PI will immediately notify; in writing, the funding agency, if applicable, any action resulting in a temporary or permanent suspension of the study.
A copy of this correspondence will also be forwarded to the DSMB and the SRC.

12.0 ADDITIONAL SAFETY REPORTING REQUIREMENTS

Safety Reporting to Amgen

The Investigator is responsible for compliance with expedited reporting requirements for serious, 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 8 and Table 9 below. Individual safety reports (Table 8) should be accompanied by the Fax Cover Form provided in Appendix C, and sent to Amgen Global Safety, utilizing the fax or email information provided on the cover page. Aggregate safety reporting (Table 9) including listings, tabulations and summary reports should be scanned and accompanied by the Fax Cover Form provided in Appendix C, and sent to Amgen NASCR, utilizing the email information provided on the cover page. In addition to the requirements outlined in Table 8 and 9, 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 13.0 'Accidental Exposures to Talimogene Laherparepvec and Herpetic Events').

Table 8. 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 C for Amgen template forms)

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

Table 9. 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 any body 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 any body 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 C

13.0 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 10 Accidental Exposure and Herpetic Event Reporting Requirement Summary'.

13.1 Accidental Exposure of HCPs to Talimogene Laherparepvec

HCPs involved in your clinical trial who were directly exposed to talimigene 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).

13.2 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.

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**. 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 provider to facilitate reporting to Amgen. Suspected herpetic lesions should be reported by the personal provider 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 10. Accidental Exposure and Herpetic Event Reporting Requirement Summary

Exposed Person	Reporter	Timeframe for Reporting to Amgen	Report Mechanism	Timing of Swab Collection	qPCR Testing Required ?	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	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	Close Contact's Personal Physician	Close Contact's Personal Physician and Amgen

13. QUALITY ASSURANCE MEASURES

Per the UACC DSMB Charter, Internal Ad Hoc audits may be performed on any UACC clinical trial if identified for audit, the audit will be conducted by an identified audit team per the UACC DSMB Charter. A QA/QC representative will coordinate the audit team functions and a written audit report will be provided to the principal investigator and the DSMB

14. MODIFIED RECIST CRITERIA – Appendix B

15. REMOVAL OF SUBJECTS

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the provider or at the institution. If this occurs, the investigator, or designee, is to discuss with the subject the safe and appropriate processes for discontinuation from the investigational product, intervention or device.

Subjects that wish to discontinue active IP treatment/intervention/device may elect to continue with the other protocol required assessments. The investigator should discuss with the subject the options for continuation of the study schedule of assessments (i.e. blood work, scans, physical exams, diaries) and collection of data, including endpoints and adverse events.

The investigator or designee must document the change in status of the subject's participation in the study and as applicable, the level of follow up that is agreed to by the subject (i.e. agrees to follow up exams, adverse event review, phone contact, but not to further treatment and/or procedures).

Subject withdrawal of consent for a study indicates that the subject does not wish to receive further protocol required therapies or procedures, and the subject does not wish to, or is unable to continue further study participation. Subject data only up to the time when consent is withdrawn will be included in the analysis of the study.

16. STATISTICAL CONSIDERATIONS

16.1 Analysis Endpoints

16.1.1 Primary Endpoint

The primary end point is to evaluate the overall response rate (ORR) defined as proportion of subjects who achieved CR and PR in the cSCC TILs. Clinical assessments will be done using a ruler or calipers. Digital photograph of the lesion(s) will be recorded each visit. Through clinical evaluation, CR will be defined as the complete disappearance of all TILs and PR will be defined as at least a 30% decrease in the sum of the diameters of TILs, taking as reference the baseline sum diameters. Progression is defined as >20% increase of at least 5 mm in the sum of the longest diameters of the TILs compared with the smallest sum of the longest diameter recorded or increase in tumor burden ≥ 20% relative to nadir (minimum recorded tumor burden) or the appearance of recurrent lesions confirmed by an assessment 8 weeks after the end of the injections (Visit 6). Stable disease (SD) is defined as decrease in tumor size <30% or an increase in size <20%.

16.1.2 Secondary Endpoints

1. To assess the safety and adverse effect profile of talimogene laherparepvec in low risk cSCC. Adverse events to be assessed according to National Cancer Institute Common Terminology. This will be determined by incidence of all adverse events (AEs), grade ≥ 3 AEs, safety adverse events (SAEs), and events requiring the discontinuation of study drug, local effects on the tumor (ie, pain, inflammation and ulceration), and any clinically significant laboratory values.

2. Time to response in cSCC TILS. Time to response is the time from first visit until objective tumor response (CR or PR) is identified

3. Duration of overall response (DOR) of TILs. This will be measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or progressive disease (PD) is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started. If no recurrence or PD is documented after PR or CR is observed the time measurement will be performed at Visit 8.

4. Durable response rate of TILs. The duration of overall response is ORR lasting continuously for > than or equal to 6 months.

5. Time to progression (TTP) of TILs. This will be measured from the time treatment is initiated until the first date that recurrence or progressive disease (PD) is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

6. Overall response rate (CR+PR) of TILs assessed by imaging technique (high frequency ultrasound) and correlate it with clinical overall response rate.

7. Overall clinical response rate (CR+PR) of individual TILs injected with talimogene laherparepvec (not as overall subject response). Overall response rate is defined as the proportion of injected lesions which achieved complete and partial response.

8. Overall clinical response rate (CR+PR) in cSCC TNILs. Overall response rate is defined as the proportion of subjects who achieved complete and partial response in TNILs. cSCC TNILs will be categorized by distance to TILs. Group 1: < 5 cm, Group 2: 5 to 15 cm, Group 3: >15 cm. Response rates in TNILs will be measured using a ruler or calipers. Digital photograph of the lesion will be recorded each visit. Complete response of TNILs will be defined as the disappearance of all TNILs and partial response defined as at least a 30% decrease in the sum of the diameters of TNILs, taking as reference the baseline sum diameters. Progression is defined as 20% increase of at least 5 mm in the sum of the longest diameters of the TNILs compared with the smallest sum of the longest diameter recorded or increase in tumor burden ≥ 20% relative to nadir (minimum recorded tumor burden). Stable disease (SD) is defined as decrease in tumor size <30% or an increase in size <20% that is less than 5 mm in the sum of the longest diameters of the TNILs compared with the smallest sum of the longest diameter recorded.

16.1.3 Exploratory Endpoint

The exploratory endpoint is to quantify the abscopal effect experienced by participants after their injections. Participants' charts will be reviewed to assess the number of nonmelanoma skin cancers before and after the intervention. The frequency of NMSCs before the intervention will include the 12 month and 24 month period before the first injection visit (or Visit 1). The frequency of NMSCs after the intervention will include the 12 months after the last injection visit (or Visit 4) and then 24 months after the last injection (or Visit 4) if available.

16.2 Statistical Analysis

Any patient who was treated with at least 1 dose of talimogene laherparepvec therapy will be included in safety and efficacy analysis. Descriptive statistics (mean, median, standard deviation, 25th percentile, 75th percentile, and range) will be presented for continuous variables, such as age. Frequency counts will be presented for categorical variables such as sex and race.

16.2.1 Overall Response Rate (ORR)

The analysis of ORR will use a Simon two-stage optimum design to test that the proportion with ORR is $\geq$ 80% (alternative hypothesis) versus ORR $\leq$ 50% (null hypothesis). In the first stage, 7 patients will be recruited. If $\leq$ 4 have ORR the trial will be terminated. If 5 or more have ORR, accrual will continue to the second stage. In the second stage, an additional 13 patients will be recruited. At the end of the second stage, if $\geq$ 14 patients have ORR then TVEC will be considered promising for further study. This design yields 80% statistical power with a one-sided alpha level of 0.05.

16.2.2 Safety and Adverse effects of talimogene laherparepvec in cSCC

Summary statistics (counts, percentage, mean, standard deviation, etc.) will be presented for the safety and adverse endpoint as appropriate. Grading of adverse effects will be done as per CTCAE 4.03 grading of the National Cancer Institute.

16.2.3 Duration of overall response (DOR) of TILs.

Once a PR or CR has been established, the analysis will consist of Kaplan-Meier estimates. The analysis will also include a median and a 95% 1-sided exact confidence interval.

16.2.4 Durable Response Rate of TILs.

Once a PR or CR has been established, the analysis will consist of Kaplan-Meier estimates. We will consider durable response when continuously PR or CR is sustained for at least 6 months. The analysis will also include a median and a 95% 1-sided exact confidence interval.

16.2.5 Time to progression (TTP) of TILs.

The analysis of time to response will consist of Kaplan-Meier estimates. The median time and 95% confidence interval will be presented.

16.2.6 Time to response in TILs

The analysis of time to response will consist of Kaplan-Meier estimates. The time to response data will be censored on those who do not respond at their last follow-up. The median time and 95% confidence interval will be presented.

16.2.7 Overall response rate (CR+PR) in TNILs

For each group, we will use a Simon two-stage optimum design to test that the proportion with ORR is $\geq$ 80% (alternative hypothesis) versus ORR $\leq$ 50% (null hypothesis).

16.2.8 Chart Review of Abscopal Effect

Summary statistics (counts, percentage, mean, standard deviation, etc.) will be presented for exploratory endpoint as appropriate. Statistical comparison of the number of non-melanoma skin cancers in the 12 month and 24 month period prior to the TVEC injections versus the number in the 12 months after the TVEC injections will be performed using the Wilcoxon Rank Sum Test.

16.3 Interim Analysis

In the first stage, the data will be evaluated in an ongoing manner and the investigators will be notified by the biostatistics team when: a. five subjects have demonstrated ORR or b. a total of 7 subjects have been recruited and $\leq$ 4 of them demonstrate ORR.

17. ANALYSIS

17.1 Safety Analysis –see #16

17.2 Efficacy Analysis –see #16

17.3 Interim Analysis – see #16

18. REGULATORY OBLIGATIONS

18.1 Informed Consent

Before a subject's participation in the clinical study, the investigator or identified designee is responsible for obtaining written informed consent from the subject or legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specified procedures, investigational product, intervention or device are administered or initiated.

18.2 Institutional Review Board

A copy of the protocol, proposed ICF, and all other applicable subject information will be submitted to the IRB for written approval. A copy of the written approval of the protocol and ICF must be on file at the institution before recruitment of subjects into the study.

The investigator is responsible for obtaining IRB approval/renewal at least annually throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be on file at the institution.

The investigator must submit study information to the IRB as required by all applicable guidelines and requirements. The investigator will obtain IRB approval for subsequent protocol amendments; except changes to eliminate an immediate hazard to study subjects, and changes to the informed consent document from the IRB prior to implementation.

The investigator will notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other serious adverse event reports occurring at or received from participating centers as applicable for multi-center trials following the IRB policies and procedures.

19. ADMINISTRATIVE PROCEDURES

19.1 Investigator Responsibilities

The PI will conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, FDA regulations, local IRB and legal requirements.

19.2 Data and Safety Monitoring Board Protocol Review

Initial DSMB protocol review will be conducted prior to SRC and IRB submissions.

Any protocol revision or amendment that includes a potential change to any section of data and safety monitoring plan must be reviewed and approved by the DSMB ***prior to*** **the protocol amendment submission to the IRB**.

19.3 Multicenter Trials- Does not apply to this study

19.3.1 UACC DSMB and QA/QC Monitoring

19.3.2 Alternate DSMB Oversight

20. SUBJECT CONFIDENTIALITY

The principal investigator will ensure that the subject's confidentiality is maintained in compliance with Federal regulations, the International Conference on Harmonization (ICH), and Good Clinical Practice (GCP) Guidelines.

Oversight entities and/or regulatory authorities will be permitted direct access to review the subject's original medical records, electronic medical records or certified copies for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

21. STUDY DOCUMENTATION AND ARCHIVE

The investigator will maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Delegation of Responsibilities Form.

Source documents, data, and records from which the subject's CRF data are obtained include, but are not limited to, hospital records, clinical/office/research charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source data will include information necessary for the reconstruction and evaluation of the trial.

The principal investigator or sponsor-investigator is responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation as required per ICH Guidelines. This can be accomplished by the PI, through the site's standard operating procedures and/or the institutions infrastructure.

The investigator will follow ICH Good Clinical Practice Guidelines and the Code of Federal Regulations for records and record retention.

22. DATA

Applicable data as specified as required in the protocol will be reported/submitted in the case report form (CRF). Data reported in the case report forms that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. **CRFs will be completed via the UACC OnCore.**

Additional procedures and assessments may be performed as the institution's standard of care; however these data should remain in the medical records and should not be provided as part of the clinical study data unless it pertains to a serious adverse event.

The investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational product/intervention/device, or employed as a control in the investigation.

23. PROTOCOL DEVIATIONS

The investigator will conduct the study in conformance with this protocol, generally accepted standards of Good Clinical Practice and all applicable federal, state and local laws, rules, and regulations.

Approvals or waivers for protocol deviations will be obtained from the sponsor-investigator ***prior to*** occurring, except changes to eliminate an immediate hazard to study subjects. If immediate verbal approval is obtained, it will be documented by the research staff obtaining the approval and followed by a written protocol deviation form per the site standard operating procedures. The sponsor or the sponsor-investigator will sign the Protocol Deviation (Waiver) Approval Form or other similar document. The original will be filed in the regulatory binder and a copy will be placed in the subject's research file.

24. ECOG- does not apply to this study

25. COMMON TOXICITY CRITERIA (CTCAE)

CTCAE Version 4 will be used as reference to document AEs that occur in the study.

26. STUDY SCHEDULE

Test or Procedure	Screening Visit 0	Treatment Visit 1	Treatment Visit 2	Treatment Visit 3	Treatment Visit 4	Follow-up 1- Visit 5	Follow-up 2 Visit 6	Follow-up 3 Visit 7	Follow-up 4 Visit 8	Telephone Follow-up	Early Term Visit
Informed consent	X										
Medical history [1]	X										
Concurrent meds	X	X	X	X	X	X	X	X	X		X
Vital Signs	X	X	X	X	X	X	X	X	X		X
Physical Exam	X										
Hematology [2]	X			X							X
Serum chemistry [3]	X			X							X
Urine or serum pregnancy test	X										
Tumor evaluation [4]	X	X	X	X	X	X	X	X	X		X
Tumor Ultrasound after visit[5]	X						X				
Skin biopsy	X										
Adverse event evaluation [6]		X	X	X	X	X	X	X	X		X
IPTreatment Intervention Device (syringe)		X	X	X	X						
Telephone Assessment[7]										X	

1 = Complete medical history will include demographics
2 = Hematology to include CBC, differential and platelet count
3 = Chemistry to include chemistries, liver function tests
4 = Tumor measurements, photographs
5 = Tumor ultrasound will only be performed for patients enrolled at UACC
6 = AE recording will begin on Visit 1 of the IP treatment/intervention/device
7 = Verbal assessment of changes of target lesions

27. GLOSSARY - Not applicable

28. DEFINITIONS- Not applicable

29. REFERENCES

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3. Rogers HW, Weinstock MA, Harris AR, Hinckley MR, Feldman SR, Fleischer AB, Coldiron BM. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Archives of dermatology. 2010;146(3):283-7.
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7. Miller SJ, Alam M, Andersen J, Berg D, Bichakjian CK, Bowen G, Cheney RT, Glass LF, Grekin RC, Kessinger A. Basal cell and squamous cell skin cancers. Journal of the National Comprehensive Cancer Network. 2010;8(8):836-64.
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30. APPENDICES

30.1 Appendix A- Measurement of Lesions and Digital Photography

Digital Photographic Guidelines for Serial Photographic Documentation of cSCC Location and selected target lesions (TILs and TNILs)
• ID card with subject number, date and visit: two each
• Close-up view with millimeter scale of the target area of the selected cSCC: two each
• Global view of the target cSCC lesions area: two each

Equipment
Camera: Nikon Coolpix L127 with 16mp.

Procedures
In these clinical photographs for the duration of the study, the only variable allowed to change is the skin condition itself. Therefore, anything extraneous to the condition (furniture, etc.) is to be eliminated from the photographic field, starting at the entry visit through the final visit. The necessity of good end-of-study photographs should be stressed to patients to ensure their cooperation. Lighting, framing, and exposure must be held constant. In the end, the images should read like a time-lapse movie.

30.2 Appendix B- RECIST

Modified-Response Evaluation Criteria in Solid Tumors (RECIST1.1) Quick Reference:

Eligibility

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

> **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by histology.
>
> **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 5 mm using conventional techniques.
>
> **Non-measurable lesions** - all small lesions (longest diameter < 5 mm with conventional techniques)

Methods of Measurement –

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- Histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions (e.g. scar) and residual malignant lesions).
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Baseline documentation of Target Lesions

- All measurable lesions up to a maximum of five TILs and ten TNILs per subject should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) will be calculated and reported as the baseline sum LD for *both TILs and TNILs respectively.* The baseline sum LD will be used as reference by which to characterize the objective tumor.

Response Criteria:

Evaluation of TILs

Complete Response (CR):	Disappearance of all TILs
Partial Response (PR):	At least a 30% decrease in the sum of the LD of TILs, taking as reference the baseline sum LD
Progressive Disease (PD):	>20% increase of at least 5 mm in the sum of the longest diameters of the target lesions Or increase in tumor burden ≥ 20% relative to nadir (minimum recorded tumor burden) Or the appearance of one or more new lesions confirmed by an assessment 8 weeks after the end of the injections (Visit 6).
Stable Disease (SD):	A decrease in tumor size <30% or an increase in size <20% that is less than 5 mm in the sum of LDs of the TILs compared with the smallest sum of the LD recorded.

Evaluation of TNILs

Complete Response (CR):	Disappearance of all TNILs
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of TNILs, taking as reference the baseline sum LD
Progressive Disease (PD):	>20% increase of at least 5 mm in the sum of the longest diameters of the target lesions Or increase in tumor burden ≥ 20% relative to nadir (minimum recorded tumor burden) Or the appearance of one or more new lesions confirmed by an assessment at Visit 3.
Stable Disease (SD):	A decrease in tumor size <30% or an increase in size <20% that is less than 5 mm in the sum of LDs of the TNILs compared with the smallest sum of the LD recorded.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

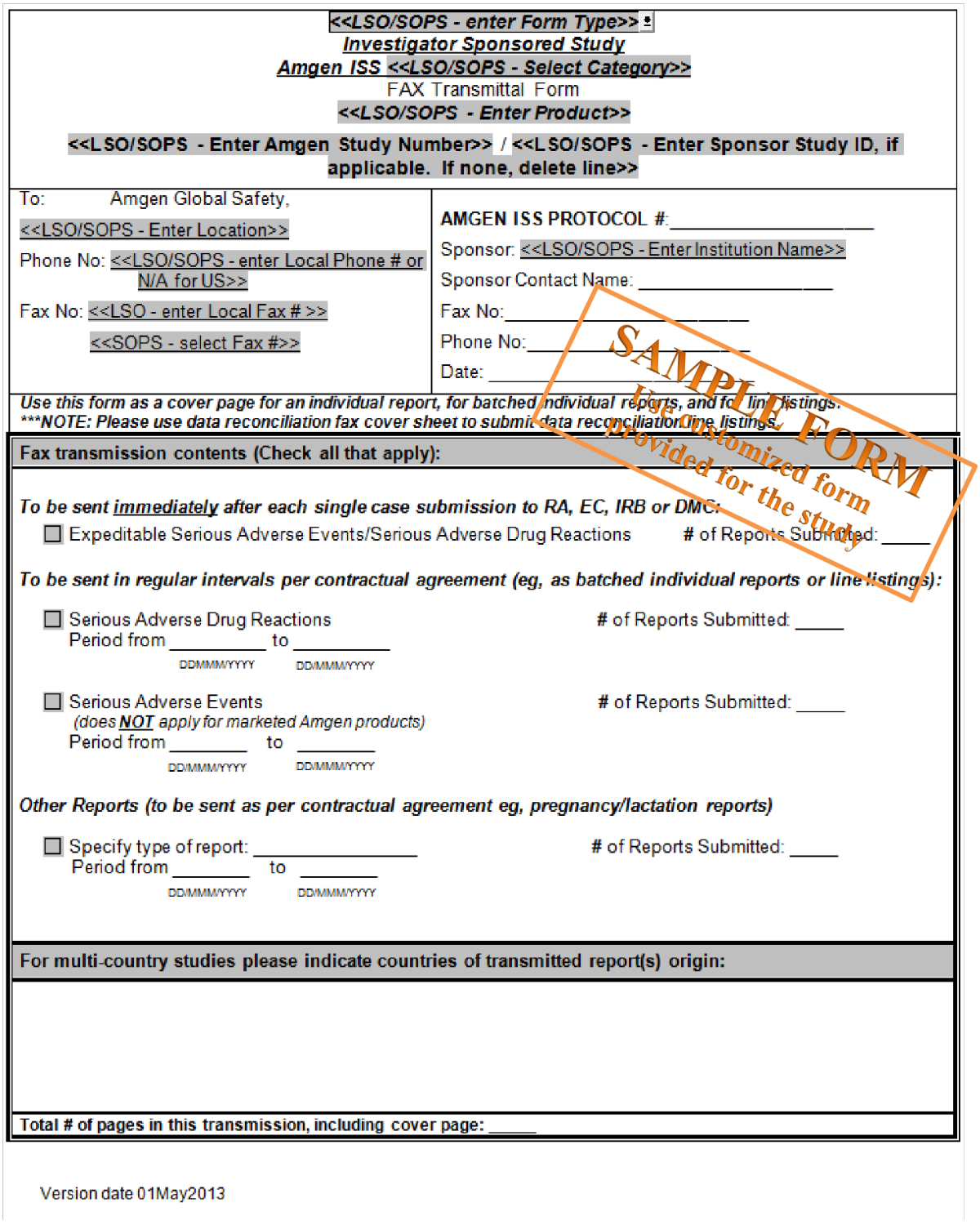
TILs	TNILs	Recurrent TILs	Overall response
CR	CR	No	CR
CR	Incomplete response/SD/PD	No	CR
PR	Any	No	PR
SD	Any	No	SD
PD	Any	Yes or No	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

30.3 Appendix C- Safety Reporting Submission Forms

Sample Fax Cover Form 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.***

SAMPLE FORM
Use customized form provided for the study

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

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

SAMPLE FORM
Use customized form provided for the study

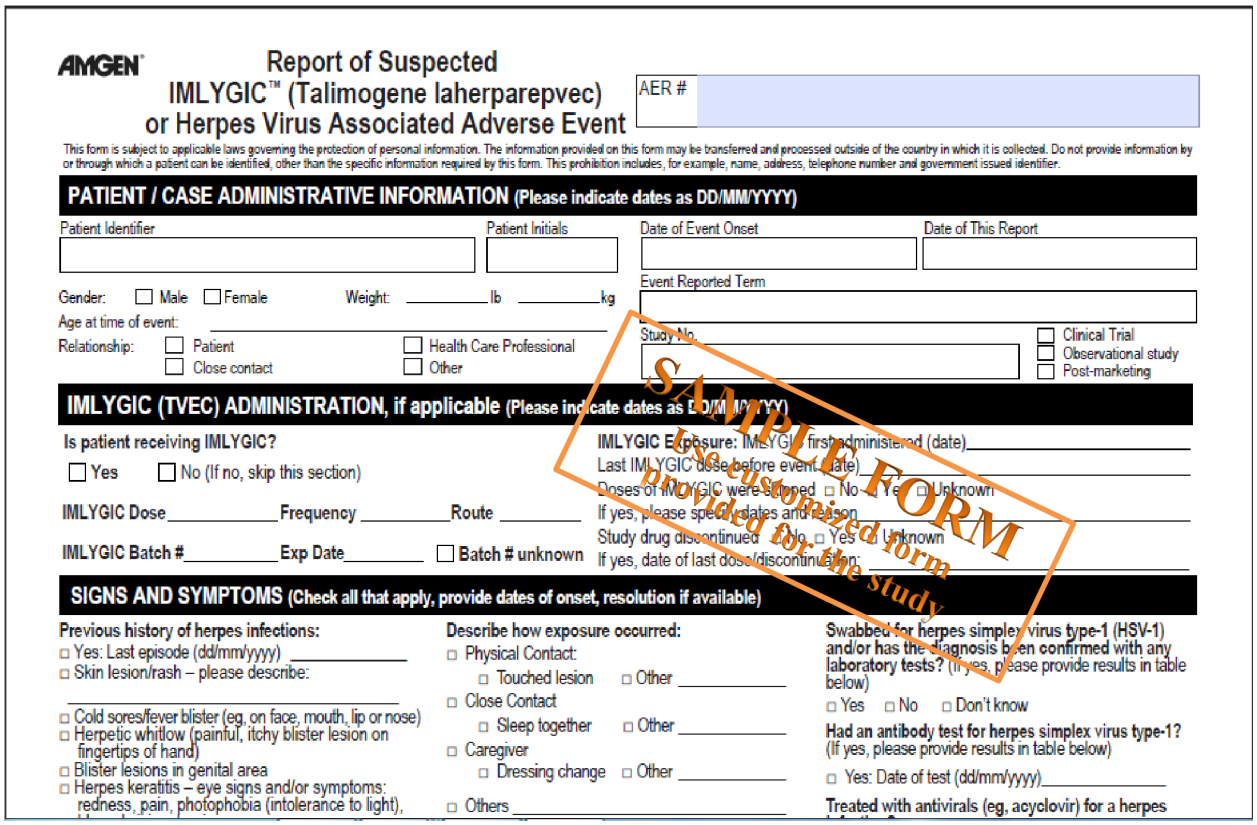
Fax transmission contents (Check all that apply):

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: _____

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



AMGEN

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

AER #

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

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

Patient Identifier | Patient Initials | Date of Event Onset | Date of This Report

Gender: ☐ Male ☐ Female Weight: _____ lb _____ kg

Age at time of event: _____

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

Event Reported Term

Study No. ☐ Clinical Trial ☐ Observational study ☐ Post-marketing

IMLYGIC (TVEC) ADMINISTRATION, if applicable (Please indicate dates as DD/MM/YYYY)

Is patient receiving IMLYGIC?

☐ Yes ☐ No (If no, skip this section)

IMLYGIC Dose _____ Frequency _____ Route _____

IMLYGIC Batch # _____ Exp Date _____ ☐ Batch # unknown

IMLYGIC Exposure: IMLYGIC first administered (date) _____

Last IMLYGIC dose before event (date) _____

Doses of IMLYGIC were skipped ☐ No ☐ Yes ☐ Unknown

If yes, please specify dates and reason _____

Study drug discontinued ☐ No ☐ Yes ☐ Unknown

If yes, date of last dose/discontinuation: _____

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

Previous history of herpes infections:

☐ Yes: Last episode (dd/mm/yyyy) _____

☐ Skin lesion/rash – please describe:

_____

☐ Cold sores/fever blister (eg, on face, mouth, lip or nose)

☐ Herpetic whitlow (painful, itchy blister lesion on fingertips of hand)

☐ Blister lesions in genital area

☐ Herpes keratitis – eye signs and/or symptoms: redness, pain, photophobia (intolerance to light),

Describe how exposure occurred:

☐ Physical Contact:
- ☐ Touched lesion ☐ Other _____

☐ Close Contact
- ☐ Sleep together ☐ Other _____

☐ Caregiver
- ☐ Dressing change ☐ Other _____

☐ Others _____

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

☐ Yes ☐ No ☐ Don't know

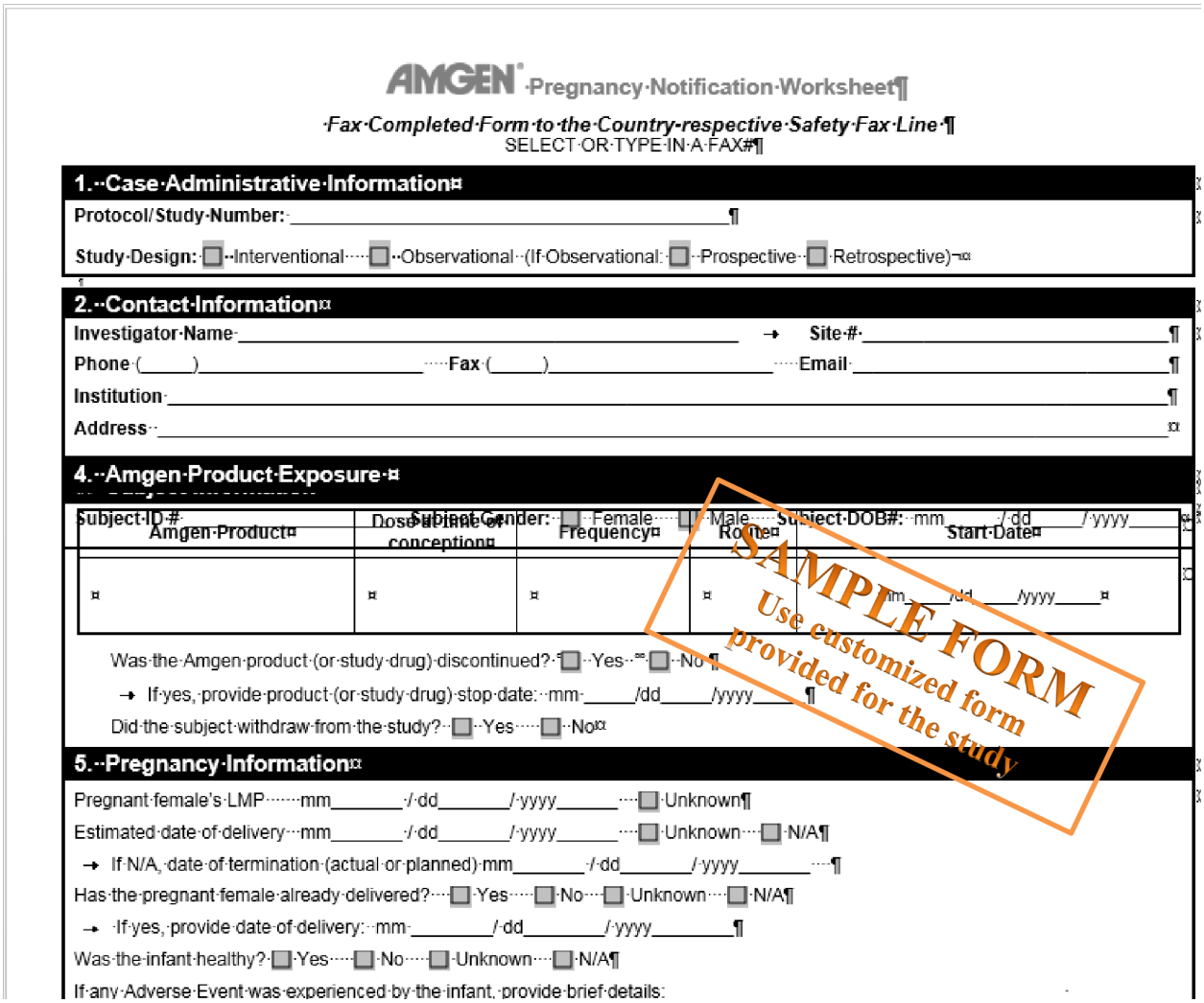
Had an antibody test for herpes simplex virus type-1? (If yes, please provide results in table below)

☐ Yes: Date of test (dd/mm/yyyy) _____

Treated with antivirals (eg, acyclovir) for a herpes

SAMPLE FORM
Use customized form provided for the study

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··_____¤

4.··Amgen·Product·Exposure·¤

Subject·ID·#·_____ Subject·Gender:·☐··Female·····☐··Male·····Subject·DOB#:·mm_____/dd_____/yyyy_____¤

Amgen·Product¤	Dose·at·time·of·conception¤	Frequency¤	Route¤	Start·Date¤
¤	¤	¤	¤	mm_____/dd_____/yyyy_____¤

SAMPLE FORM
Use customized form provided for the study

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_____····¶

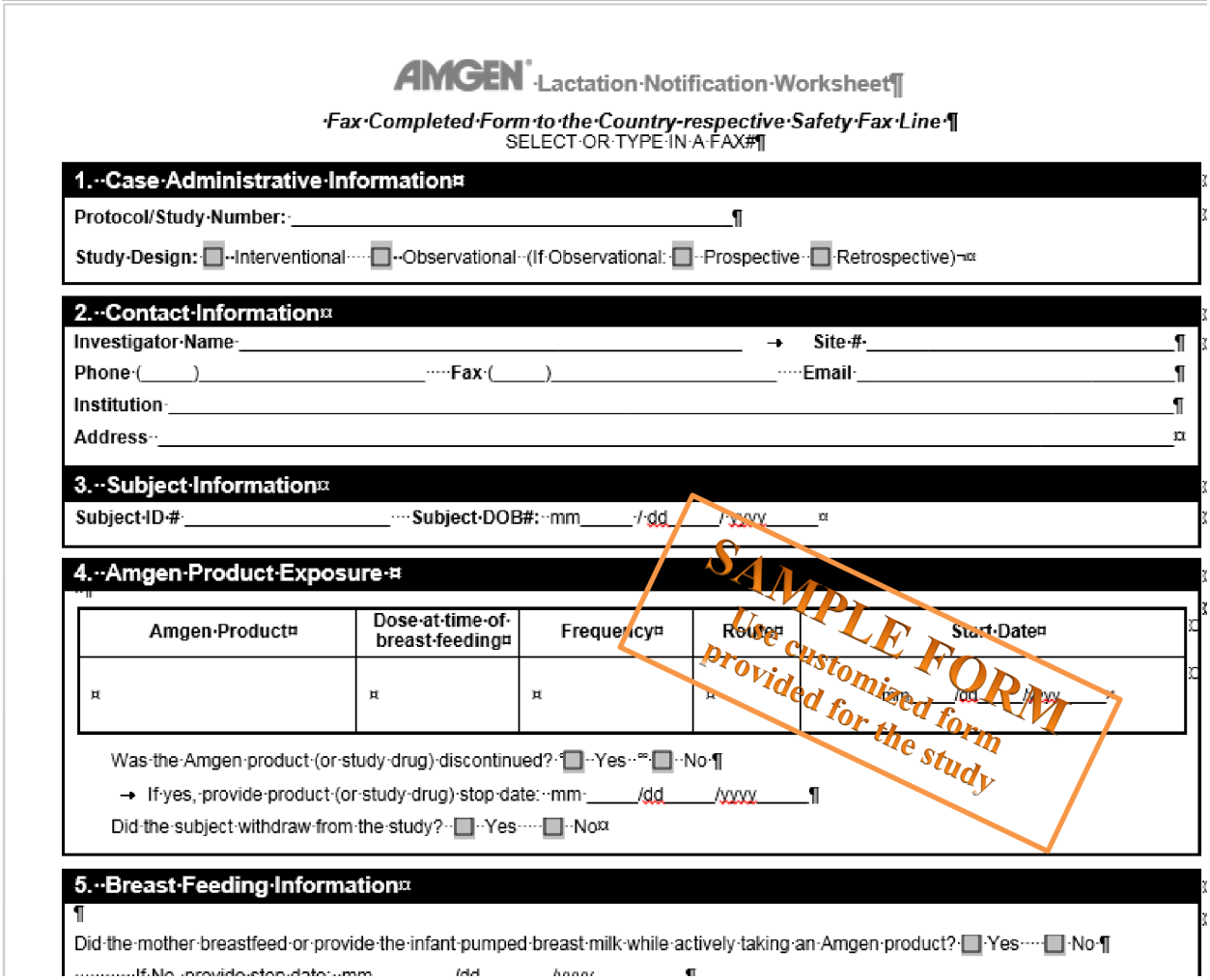
Has·the·pregnant·female·already·delivered?····☐·Yes·····☐·No····☐·Unknown····☐·N/A¶

→ ·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:

Sample of Lactation Notification Worksheet



AMGEN ·Lactation·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·DOB#:··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¤

SAMPLE FORM
Use customized form provided for the study

5.··Breast·Feeding·Information¤

¶

Did·the·mother·breastfeed·or·provide·the·infant·pumped·breast·milk·while·actively·taking·an·Amgen·product?·☐·Yes·····☐·No·¶

·····If·No,·provide·stop·date:··mm_____/dd_____/yyyy_____¶