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Title of Project: A Phase I Study of Talimogene Laherparepvec and Panitumumab in Patients with Locally Advanced Squamous Cell Carcinoma of the Skin (SCCS)

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Official Title:	**A Phase 1 Study of Talimogene Laherparepvec and Panitumumab in Patients with Locally Advanced Squamous Cell Carcinoma of the Skin (SCCS).**
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PROTOCOL AMENDMENTS

The current version of the protocol was released on 09-09-2020 and includes the following Amendments, 1-18 into the version approved by Rutgers IRB on 09/05/2019.

Amendment #	Section	Page(s)	Protocol Change
1	1.3	9	Insertion: Patients who are not eligible for surgery are only allowed to continue protocol therapy past 3 cycles if clinical benefit, defined as partial response (PR), or stable disease (SD), is achieved. This also assumes that separate systemic options are not available for patient after protocol therapy of 3 cycles.
2	1.3	10	"Peripheral blood will be collected on day 1, day 22, day 36, and on the day of tumor resection" is replaced with "Peripheral blood will be collected prior to treatment, at the time of definitive surgery or biopsy, and at the time of progression, if applicable".
3	1.3.1; Table 1	10-11	IHC and Flow Cytometry at Day 64 deleted. "Baseline labs within 14 days of treatment" is replaced with "Baseline labs, blood tests, and EKG (electrocardiogram), need to be done within 14 days of treatment".
4	1.7.2.1	17	"Panitumumab is an FDA-approved agent for use in SCCS" is replaced with "Panitumumab is FDA-approved for use in patients with wild-type RAS (defined as wild-type in both K-RAS and N-RAS as determined by an FDA-approved test) metastatic colorectal cancer (mCRC)."
5	1.7.5.4	22	Text in "Table 6: Clinical Handling Times Outside Labelled Storage Conditions" modified. "48 hours (inclusive of 16 hours maximum in the syringe)" modified to "48 hours (inclusive of 8 hours maximum in the syringe)"
6	1.7.5.4	24	Duplicate bullet under Figure 3 "o *Avoid premature extraction of needle c" deleted
7	1.7.6.3	27	Several changes made to Table 8
8	1.7.6.3	28, 29	A New Table, "**Table 10. Algorithm for Dose Modifications for Infusion Reactions"** was added
9	1.7.6.3	29	Other toxicities of panitumumab were added as sub-item 9)" under section 1.7.6.3
10	1.7.9	32	**Added Section 1.7.9** **Dose-Limiting Toxicity** Dose-limiting toxicity is defined as any occurrence of CTCAE grade 3 or greater adverse event in four weeks following the administration of the study products except grade 3 laboratory values not deemed clinically significant, grade 3 fatigue which resolves within 72 h of holding or modifying protocol therapy and grade 3 rash, as the latter is an already known potential side effect of panitumumab.
11	1.7.9.1	32	**Added section "1.7.9.1 Talimogene laherparepvec DLTs"**
12	1.7.11	33	**Added Section 1.7.11**

Amendment #	Section	Page(s)	Protocol Change
			Staggering Interval between the First Three Consecutive patients The staggering interval between the first three consecutive patients will be 2 weeks past the first infusion of the combination therapy (Cycle 1,Day 21). The staggering interval of 2 weeks was based on the median time to the development of dermatologic or most severe skin/ocular toxicity of 15 days after the first dose of panitumumab (US Package Insert, panitumumab Solution for Intravenous Infusion, 2006).
13	1.8.1.2	34	"all patients will have peripheral blood samples collected prior to treatment, at the time of definitive resection or post-treatment, at restaging time points and at the time of progression, if applicable" is replaced with "all patients will have peripheral blood samples collected prior to treatment, at the time of definitive surgery or biopsy, and at the time of progression, if applicable".
14	6.1.2	43	"We plan to start monitoring the treatment safety after 5 patients are recruited." Was replaced with "We will employ a 3 + 3 study design in the first six patients enrolled. This will allow for early detection of unexpected safety signals and will allow for rapid implementation of measures to diminish the risk of toxicity to subsequently enrolled subjects." Added the statement "The interim safety assessment will start and includes the rules of the 3+3 design based on the incidence of DLTs." "We plan to start monitoring the treatment safety after 5 patients are recruited." was modified to "We plan to continue monitoring the treatment safety after the first 6 patients are recruited."
15	6.1.5.2	47	The text under **"Section 6.1.5.2 Reporting SAEs using commercially available drugs"** modified.
16	1.3.1	11	Table 1 to reflect footnote 1 addition "Following surgery, patients will have radiographic assessments every 12 weeks to monitor disease status."
	1.3.2	11	Revised to read: "[…] after 9 weeks of study treatment, then every 12 weeks following surgery to monitor disease status."
	1.8.1	33	Added: Specimen, including tissue and blood, will be banked for the studies described below and for potential future studies. Specimens will be analyzed once funding becomes available.
	4.8.2	41	Removed patient compensation. Revised to read: Subjects will not be compensated for participation in this research study.
17			Principal Investigator changed to Adam Berger, MD
	1.1	9	Revised to read: The overall treatment strategy described in this protocol is to treat locally advanced/unresectable SCCS with at

Amendment #	Section	Page(s)	Protocol Change
			least **3 cycles** of talimogene laherparepvec in combination with panitumumab, and monitor patients for disease response.
	1.8.1.1	34	**Laboratory Evaluations and Procedures/Correlative Studies: Overview of Possible Molecular Investigations** modified. Added: Tumors will be stored frozen in RNAlater media, and total RNA will be extracted to identify gene expression changes within the tumor and variations in immune cell populations using a CyberSort strategy.
	1.8.1.1	35	Added: and flow cytometry will be performed on cells isolated from peripheral blood
	1.8.1.1	36	Added: Part of the tumor sample will be placed in complete media on wet ice
18	Figure 1	11	Updated Figure 1 Study Design
	Table 1	11	Revised Table 1 headings to read: Day 22 (Week 4) Day 36 (Week 6) Post- surgery or Bx follow up[9] Follow up (every 12 weeks for 2 years[10]
	Table 1	12	Added: 9- Post-surgical follow up visit (14-28 days from surgery) or post-biopsy visit (30 days from biopsy)
	Table 1	12	Added: 10- Follow up imaging and visits should be measured from the time of surgery or biopsy, if considered unresectable. The window for blood draws/visits/scans during follow up is ± 7 days.
	2.4	37	Added: and Duke University Medical Center - Duke Cancer Center
	4.1 B	38	Added: and Duke University Medical Center - Duke Cancer Center

Amendment #	Section	Page(s)	Protocol Change
19	Figure 1	12	Updated Figure 1 Study Design
	Table 1	13	Modified: Footnote 10 ± 7 days changed to ± 14 days. Added: CBC with Differential requirement for Day 1 Added: CBC with Differential, Basic Metabolic Panel + Mg, and Hepatic Function Panel requirement forDay 22
	1.3.2	14	Added: If a patient undergoes surgery after 3 cycles of TVEC and is rendered disease-free at the time of surgery, they will considered a clinical complete response (NED-no evidence of disease). If this is the case, there will be no index lesion to follow on subsequent imaging and thus no need for RECIST criteria assessment. These patients will be followed by clinical exam as well as the standard imaging outlined in Table 1. If they develop a biopsy-proven recurrence of their disease, they will be considered a treatment failure and come off study. If a patient undergoes surgery but continues to have an index lesion that can be followed by RECIST assessment, this lesion will continue with response assessments.
	1.7.4.1	19	Modified: 100 mg changed to 1000 mg
	2.4	38	Added: and and NYU Langone Health.
	4.1.B	39	Added: and and NYU Langone Health
20	Table 1	13	Added to footnote 10: After one year of follow-up, if patient remains without evidence of recurrence, subsequent follow-up will be at the discretion of the treating investigator but should not be less frequent than every 6 months for the second year of follow-up.
21	1.8.1.1.	36	Added: Samples will be transferred to NYU for analysis. Deleted: by the Cancer Institute Immune Monitoring Shared Resource Facility
	1.8.1.2.	37	Deleted: the Cancer Institute Immune Monitoring Shared Resource Facility
	1.8.1.3.	38	Added: Samples will be transferred to NYU for analysis.
	2.4	39	Deleted: in the Immune Monitoring Shared Resource Facility at the Rutgers Cancer Institute of New Jersey Added: at NYU Langone Health

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10.0 Appendices

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List of Abbreviations

5-FU	5-Fluorouracil
ADCC	Antibody dependent Cell-mediated Cytotoxicity
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APCs	Antigen Presenting Cells
AST	Aspartate Aminotransferase
BRS	Biospecimen Repository Service
BSL	Biosafety level
BUN	Blood urea nitrogen
CBC	Complete blood count
CINJ	Cancer Institute of New Jersey
CINJOG	Cancer Institute of New Jersey Oncology Group
cm	Centimeter
CR	Complete response
CRF	Case Report Form
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Lymphocyte
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
HCP	HealthCare Professional
HHS	Department of Health and Human Services
HSV	Herpes Simplex Virus
ICH	International Council for Harmonization
IFN-γ	Interferon gamma
IHC	Immunohistochemistry
IRB	Institutional Review Board
irPFS	Immune-related Progression-free Survival
irRC	Immune-related Response Evaluation Criteria in Solid Tumors
IVIG	Intravenous immunoglobulin
kg	kilograms

LD	Longest Diameter
mcg/µg	Micrograms
MHC	Major Histocompatibility Complex
mL	milliliters
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIH	National Institutes of Health
NK	Natural Killer
OHRP	Office of Human Research Protection
OHRS	Office of Human Research Services
OS	Overall Survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-L1	Programmed Death-Ligand 1
PET	Positron Emission Tomography
PFU	Plaque Forming Unit
PHI	Protected health information
PI	Principal Investigator
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RWJUH	Robert Wood Johnson University Hospital
SAE	Serious adverse event
SCCS	Squamous Cell Carcinoma of the Skin
sCr	Serum creatinine
SD	Stable disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper limit of normal
USP	United States Pharmacopeia
µm	Micrometer

1.0 Research Design

1.1 Purpose/Specific Aims

The purpose of this protocol is to serve as a phase I/II study of talimogene laherparepvec in combination with panitumumab in locally advanced or metastatic squamous cell carcinoma of the skin (SCCS). The primary hypothesis is that panitumumab, an antibody against Epidermal Growth Factor Receptor (EGFR), exhibits antitumor activity in patients with advanced squamous cell carcinoma of the skin and it may be enhanced when combined with talimogene laherparepvec, a HSV-1–derived oncolytic immunotherapy designed to selectively replicate within tumors and produce granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance systemic antitumor immune responses, when delivered preoperatively. The overall treatment strategy described in this protocol is to treat locally advanced/unresectable SCCS with at least 3 cycles of talimogene laherparepvec in combination with panitumumab, and monitor patients for disease response. Patients will go on to surgical resection if adequate disease response is achieved; otherwise, patients who are receiving clinical benefit will be allowed to continue therapy. We will assess the safety, clinical efficacy and pathologic responses to treatment with talimogene laherparepvec in combination with panitumumab. The prospect is that the data derived from this study will lead to a large randomized trial testing the efficacy of this approach in this disease if this approach is tolerable with evidence of clinical efficacy, and that the correlates described in this protocol will identify potential candidate biomarkers of response to combination therapy.

A. Objectives

Primary:

1) To determine the safety of the combined treatment of talimogene laherparepvec and panitumumab.
2) To determine the preliminary efficacy of the combined treatment of talimogene laherparepvec and panitumumab, in comparison to single-agent panitumumab by historical control.

Secondary:

1) To assess the clinical efficacy of panitumumab in combination with intratumoral talimogene laherparepvec in terms of immune-related progression-free survival (irPFS) at 12 months, PFS hazard ratio, overall response rate (ORR), 1-year survival, overall survival (OS) and time to resectability.
2) To measure the pathologic complete response rate to panitumumab combined with talimogene laherparepvec.
3) Assess the response of injected and non-injected tumor deposits after panitumumab and talimogene laherparepvec.
4) Assess the time to initial response.
5) Assess the durable response rate.
6) To analyze the following molecular correlates with response to therapy to confirm mechanism of action, and identify potential future targeted strategies and biomarkers of response:
   A) Mutation load in tumor tissue by next generation sequencing
   B) DNA mutation signature in tumor tissue pre- and post-therapy by next generation sequencing
   C) mRNA signature in tumor tissue pre-and post-therapy by Nanostring technology
   D) Immune cell populations and immune profile in pre- and post-therapy tumor tissue and peripheral blood by flow cytometry and IHC

B. Hypotheses / Research Question(s)
For efficacy, we hypothesize that the combination of panitumumab and talimogene laherparepvec will improve the response rate in advanced SCCS from 25% with single agent panitumumab [1] to 47% (near doubling of response rate to justify added expense and time required for administration of second drug as well as potential for additional toxicities).

1.2 Research Significance*:*

1.2.1 Squamous cell carcinoma of the skin:

SCCS is the second most common type of skin cancer, and while precise estimates of incidence are challenging [2], it has been approximated that in the United States there are 700,000 new cases of SCCS diagnosed annually, with an estimated 3,932-8,791 deaths in 2012 [3]. In addition, the number of cases has consistently risen over the past 20 years [4, 5]. The majority of SCCS cases are localized and curable with early detection and surgery; however, the incidence of locally advanced and metastatic cases is rising, with a subset of cases paralleling the metastatic potential of malignant melanoma [3]. A study by Karia, et al., found the incidence of nodal metastases to be 3.7-5.4% [3], and although SCCS is known to metastasize to distant sites, 80% of those that metastasize localize to regional lymph nodes [6]. Survival has been documented to have an inverse correlation with both larger size and increasing number of lymph nodes involved [7, 8].

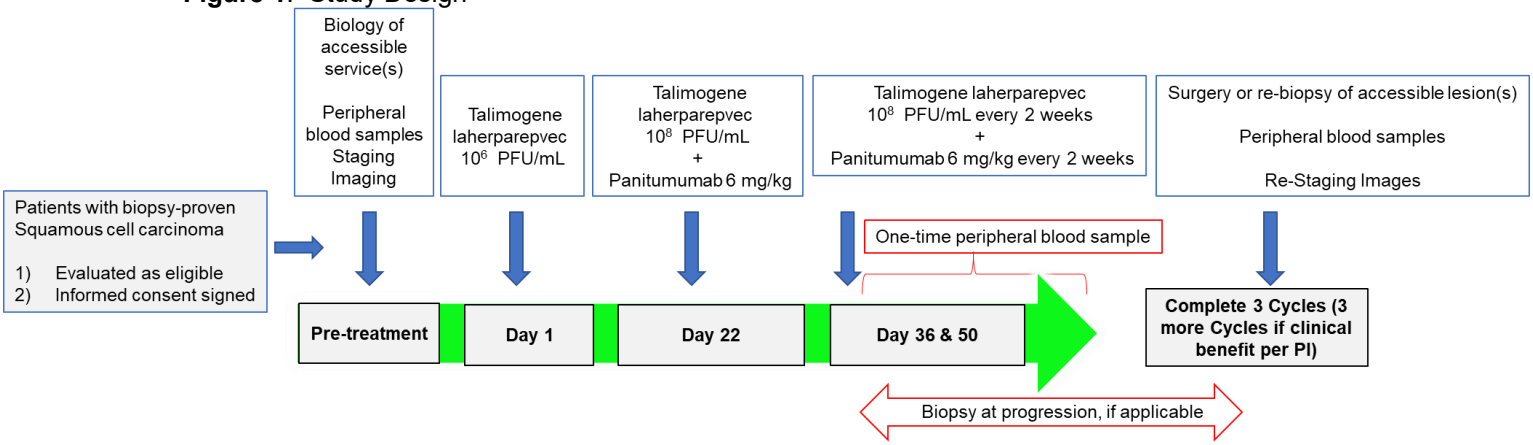
The mainstay of therapy for most cases of SCCS is surgical resection, with many surgically amenable cases easily cured [9]. However, certain high risk tumors, such as those involving bone or nerve branches, and recurrent tumors, still present a therapeutic challenge [9]. In cases of locally advanced disease or metastases to the regional lymph nodes, surgery followed by adjuvant radiation therapy has shown to improve outcomes as compared to either alone in monotherapy [10, 11]. However, treatment with radiation therapy is also associated with fatigue, nausea, vomiting and poor aesthetic or functional outcomes, important considerations in the population of older adults with comorbidities [9]. Chemotherapy is often reserved for metastatic disease or locally advanced disease not amenable to surgery or radiation. Historically, treatment decisions for patients with SCCS have been derived from regimens used in other squamous cell cancers, with suggestions of antitumor activity using regimens containing combinations of cisplatin, bleomycin, 5-fluorouracil (5-FU) and methotrexate [12-14]. However, these trials were small and not randomized, with suggestion of only modest benefit at the expense of significant toxicity [15-17]. In addition, while squamous cancers often share similar anatomic origins and histologies, SCCS likely has a unique biology driven by external insults such as ultraviolet radition, resulting in a high mutational load. Although most of these mutations are likely 'passenger mutations' that do not drive tumor growth, they may lead to protein alterations that can serve as neo-antigens which stimulate T-cell immunity, making them ideal candidates for an immunotherapy approach as has been previously reported [18].

1.3 Research Design and Methods

We plan to enroll 30 patients with locally advanced SCCS. We will collect peripheral blood and biopsy tumor tissue from all patients prior to treatment. Patients will receive an initial dose of talimogene laherparepvec 10^6 PFU/mL on day 1 to seroconvert to HSV positive to reduce the rate and severity of injection reactions. On day 22, patients will begin combination therapy with panitumumab at 6 mg/kg and talimogene laherparepvec at 10^8 PFU/mL, followed by this schedule every 2 weeks for 3 cycles. Patients will then be evaluated for surgical resection after the administration of the third cycle of combinatorial therapy (approximately day 64). Surgery may commence at this time point, or the decision may be made by surgical and medical oncologist investigators to continue therapy for up to three more cycles if it is felt that the tumor may respond further with additional therapy. Patients who are not eligible for surgery are only allowed to continue protocol therapy past 3 cycles if clinical benefit, defined as partial response (PR), or stable disease (SD), is achieved. This also assumes that separate systemic options are not available for patient after protocol therapy of 3 cycles. We will collect tumor tissue again post-treatment, either at the

time of surgical resection, if applicable, or by re-biopsy. Patients will also receive a biopsy at progression, if applicable (Figure 1). Peripheral blood will be collected prior to treatment, at the time of definitive surgery or biopsy, and at the time of progression, if applicable. Patients who are not resected but continue on protocol therapy will have PBMC sampled every three months or at progression if applicable.

Figure 1. Study Design



1.3.1 Study evaluation parameters and the schedules:

Study evaluation parameters and the schedules of assessment are presented in the Table 1. A window of +/- 3-days is allowed for all study assessments indicated on this trial except for which otherwise indicated. However, dosing windows for talimogene laherparepvec are Day 22 + 3 days for the initial dose and +/- 3 days for any subsequent cycles; dosing would be taken into account in the schedules of assessment.

Table 1. Study evaluation parameters and the schedules of assessment:

Evaluation	Pre -Tx	Day 1 (Week 1)	Day 22 (Week 4)	Day 36 (Week 6) & every 2 weeks during Tx Phase	Day 64 ± 1 week	At surgery or Bx	Post-surgery or Bx follow up[9]	Follow up (every 12 weeks for 2 years[10])	At pro-gression
History & Physical Exam ECOG PS Tumor Site Assessment	X[2]	X	X	X			X	X	X
Pregnancy Test	X[2]								
Talimogene laherparepvec Treatment		X	X	X					
Panitumumab Treatment			X	X					
Toxicity Assessment	X	X	X	X			X	X	
Photo of Tumor	X[4]				X[4]				X[4]

Surgical evaluation					X[4]				
Tumor Biopsy or Resection	X[3]					X			X[5]
CBC with Differential	X[2]	X	X	X				X	
Basic Metabolic Panel + Mg	X[2]	X	X	X				X	
Hepatic Function Panel	X[2]	X	X	X				X	
Radiographic Assessments[1]	X[1]				X[1]			X[1]	X[5]
DNA Sequencing	X[6]					X[6]			X[6]
mRNA Sequencing	X[7]					X[7]			X[7]
IHC and Flow Cytometry	X[8]					X[8]			X[8]

1- Tumor assessments as indicated by investigator (e.g. PET/CT, CT C/A/P, MRI) as needed, no more than 1 month prior to treatment. First assessment to be followed by evaluation by surgery for complete surgical resection. Photos and scans to be completed at each restaging time point. Surgeon will assess optimal timing of procedure once therapy initiated. Following surgery, patients will have radiographic assessments every 12 weeks to monitor disease status. Patients who did not have surgery will have radiologic assessments every 12 weeks.
2- Baseline labs, blood tests, and EKG (electrocardiogram), need to be done within 14 days of treatment.
3- First biopsy within 30 days of initial treatment.
4- Photo of tumor at baseline and with restaging time points. Surgical evaluation must commence. Decision may be made to proceed with 3 more cycle of systemic therapy if it is thought tumor will continue to respond.
5- Within 30 days of recurrence.
6- Partial DNA sequencing using FoundationOne™ genomic profiling will be done on tumor tissue.
7- mRNA sequencing by Nanostring nCounter system will be done on peripheral blood and tumor tissue.
8- Immunohistochemistry and targeted Flow Cytometry will be done on peripheral blood and tumor tissue.
9- Post-surgical follow up visit (14-28 days from surgery) or post-biopsy visit (30 days from biopsy)
10- Follow up imaging and visits should be measured from the time of surgery or biopsy, if considered unresectable. The window for blood draws/visits/scans during follow up is ± 14 days. After one year of follow-up, if patient remains without evidence of recurrence, subsequent follow-up will be at the discretion of the treating investigator but should not be less frequent than every 6 months for the second year of follow-up.

1.3.2 Assessing Tumor Response:

Response to combination panitumumab and talimogene laherparepvec will be assessed by RECIST criteria v 1.1 [19] shown in Table 2 as well as by immune related response criteria (irRC) [20] after 9 weeks of study treatment, then every 12 weeks following surgery to monitor disease status. The patient will have re-staging imaging as decided by the investigator to compare to the images obtained at baseline. Response will be evaluated by RECIST criteria v 1.1 for complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Patients who experience a PR or CR will have confirmatory imaging completed at 4-6 weeks. Patients who experience PD but are clinically well may be allowed to continue on study, with a confirmatory scan done 4 weeks (+/- 1 week) to determine disease status per irRC. New lesions detected by clinical assessment at a treatment visit will only trigger an unscheduled tumor response assessment if clinically indicated and felt to be in the patient's best interests by the treating investigator. If a patient undergoes surgery after 3 cycles of TVEC and is rendered disease-free at the time of surgery, they will considered a clinical complete response (NED-no evidence of disease). If this is the case, there will be no index lesion to follow on subsequent imaging and thus no need for RECIST criteria assessment. These patients will be followed by clinical exam as well as the standard imaging outlined in Table 1. If they develop a biopsy-proven recurrence of their disease, they will be considered a treatment failure and come

off study. If a patient undergoes surgery but continues to have an index lesion that can be followed by RECIST assessment, this lesion will continue with response assessments.

Table 2. RECIST Criteria v 1.1:

Response	Criteria
Complete Response (CR)	Disappearance of all target lesions; confirmed at a later time by an independent review committee or the principal investigator
Partial Response (PR)	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum (LD); confirmed at a later time by an independent review committee or the principal investigator
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions; in addition to a 20% increase above the nadir for PD, a 5-mm absolute increase is required

In determining whether or not the tumor burden has increased or decreased per irRC, the investigator should consider all target and non-target lesions as well as any incremental new lesion(s). Upon repeat imaging, PD will be confirmed if ANY of the following occur by irRC:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial diagnosis of PD is worse (qualitative assessment)
- New lesion resulting in initial diagnosis of PD is worse (qualitative assessment)
- Additional new lesion(s) since last evaluation
- Additional new non-target lesion progression since last evaluation

If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from trial therapy. Upon repeat imaging, PD will have failed to be confirmed if ALL of the following occur by irRC:

- Tumor burden is < 20 % or < 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial diagnosis of PD is stable or improved (qualitative assessment)
- New lesion resulting in initial diagnosis of PD is stable or improved (qualitative assessment)
- No incremental new lesion(s) since last evaluation
- No incremental new non-target progression since last evaluation

If repeat local site imaging fails to confirm PD by irRC and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule. When feasible, subjects should not be discontinued until PD is confirmed by the local site investigator radiology assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects who are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD.

1.3.3 Assessing Toxicity and Adverse Events:

All patients who receive one dose of protocol therapy will be evaluable for assessment of toxicity. Prior to

each cycle, the treating physician will fully assess the patient's condition with respect to possible treatment related toxicities. All adverse events, whether observed by the physician or reported by the patient, occurring during the active portion of therapy, or up to 30 days after the last dose of treatment will be graded by a numerical score according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (see http://ctep.cancer.gov/reporting/ctc.html) and recorded in the patient's medical record. For the purposes of reporting laboratory abnormalities, only Grade 3-4 adverse events will be recorded on the adverse event CRF pages. Grade 1-2 laboratory abnormalities will not be recorded on the adverse event CRF pages. Information entered on the adverse event CRF pages will include:

1) Specific type and duration of reaction (i.e., start and stop dates, resolution)
2) Severity/grade
3) Relationship to study drug (causality, attribution)
4) Management of the event, if treated with medication and other actions taken to alleviate the clinical event
5) Whether or not it was considered a SAE

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

1.3.4 Study Duration:

For each subject, this study will consist of a 28-day screening period followed by an initial dose of talimogene laherparepvec on day 1, combination therapy with panitumumab and talimogene laherparepvec on day 22 and continuing every 2 weeks for 3 cycles. Patients will then be evaluated for surgical resection after the administration of the third cycle of combinatorial therapy (approximately day 64). Surgery may commence at this time point, or investigators may continue therapy for up to three more cycles.

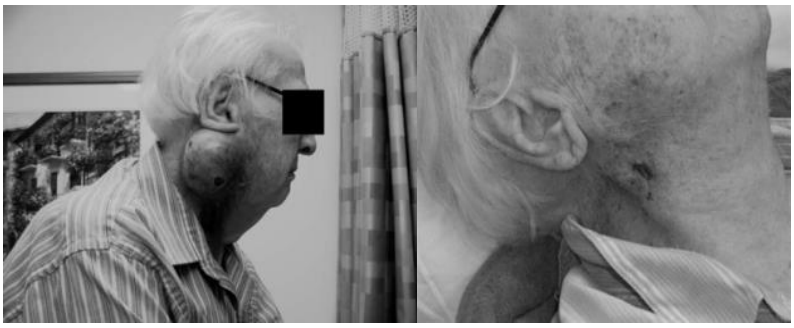
The subject's participation in the study will be considered to have ended at the time of the last visit/30 days after last drug intake. However, the patients will have a follow-up period of 104 weeks. Thus, the overall duration of the study for participants will be approximately 127 weeks. The study will be considered to have ended after the last subject has completed the last follow-up period in the study.

1.4 Preliminary Data

1.4.1 Panitumumab in SCCS:

Anti-EGFR antibodies have been shown to have activity in squamous carcinomas of the skin [21]. In 2011, Maubec, et al., studied the anti-EGFR monoclonal antibody Cetuximab in 36 patients with unresectable SCCS and found a disease control rate of 69% [22]. Multiple published case and retrospective reports have documented tumor responses in patients with SCCS treated with Cetuximab, including one from our institution demonstrating an impressive complete response in an elderly patient with SCCS [23] (Figure 2). Panitumumab, a monoclonal antibody which inhibits the activity of the EGFR, is increasingly in use for systemic treatment of patients with advanced SCCS. In addition to EGFR inhibition, panitumumab induces antibody dependent, cell mediated cytotoxicity (ADCC) [24]. Panitumumab has shown activity in squamous carcinomas of the head and neck, and lung in combination with chemotherapy and/or radiation therapy [25-28], where its addition has been demonstrated to improve both median overall survival and progression free survival with an acceptable toxicity profile. Panitumumab has been studied prospectively as a single agent in a small cohort of patients with advanced SCCS [1]. While the sample size was small, panitumumab produced impressive response rates, including a best overall response rate of 31%, a complete response rate of 12.5%, as well as a median progression free survival and overall survival of 8 and 11 months, respectively [1]. Because of the impressive responses seen in some patients such as the case reported by our institution, current NCCN guidelines for treatment of advanced SCCS disease [29] include EGFR inhibitors as an option. Nonetheless, rigorous randomized, prospective trials assessing the effectiveness of EGFR inhibitors in SCCS are lacking. Additionally, resistance may develop quickly, making studies examining combination therapies warranted [30].

Figure 2. Clinical complete response to Cetuximab in a 92-year old man. Images from left to right: Patient prior to Cetuximab and six weeks after Cetuximab. Cetuximab was administered weekly from July to October 2008. The clinical CR lasted through patient's last follow up in 2009 (7 months).



1.4.2 Talimogene Laherparepvec:
Talimogene laherparepvec is a modified HSV-1, customized into an oncolytic virus via deletion of two non-essential viral genes [31, 32] which results in attenuated viral pathogenicity, enhanced selectivity for intratumoral replication, reduced virally-induced suppression of antigen presentation and enhanced replication of HSV mutants within tumors [31, 33, 34]. Talimogene laherparepvec is additionally modified by insertion of the gene encoding for human GM-CSF, which results in the local production of GM-CSF to recruit and activate antigen presenting cells (APCs) that ultimately initiate a tumor-specific T cell response [31]. The eventual response is the induction of anti-tumor immunity both locally in infected and uninfected cells, and systemically through the priming of a tumor-specific immune response [31-33]. In early phase studies, talimogene laherparepvec demonstrated an acceptable toxicity profile, the most common side effects being low grade fevers, chills, myalgias and injection site reactions, and showed biological activity in several tumor types [35, 36]. In a phase III study of 436 patients with unresectable stage IIIb-IV melanoma, talimogene laherparepvec improved durable response rates compared to GM-CSF alone (16.3% vs 2.1%) as well as overall response rates (26.4% vs 5.7%) [31].

1.4.3 Talimogene Laherparepvec in SCCS:
Viral therapy has shown preliminary evidence of efficacy in squamous cell malignancies. The H101 adenovirus is approved in China for the treatment of head and neck squamous cell cancer based on 79% response rate when combined with chemotherapy vs a response rate of 40% with chemotherapy alone in a phase III trial [37]. Squamous skin lesions are ideal for viral therapy as they are highly amenable to intratumoral injection. In addition, SCCS is an ideal candidate for immunotherapy as it is a tumor type prone to a heavy mutation burden given its reliance on UV radiation for initiation, and research on other immunotherapies has suggested that the responses are more robust in tumors with high mutation burden [18]. Talimogene laherparepvec has a large genome with numerous nonessential genes that can be manipulated to reduce pathogenecity and improve effectiveness, and it lends itself to broad applications as the herpes virus can infect a wide range of host cells [33, 38]. Further, talimogene laherparepvec has been shown to have a tolerable safety profile, and in the context of other investigational therapies has a low rate of grade 3 or 4 adverse events, which is of particular importance when considering this patient population and the future of combined therapies [31, 35, 36].

1.4.4 Combination Talimogene Laherparepvec and Panitumumab in SCCS:
While EGFR expression is known to be high in squamous tumors [21], and impressive responses have been seen with panitumumab, only 10-20% of patients treated with EGFR inhibition have a clinical benefit.

Further, activating mutations in EGFR are rare in head and neck squamous tumors, but dramatic responses to EGFR inhibition are still seen, suggesting that other processes, such as increased ADCC activity, are at work in promoting this response [39-42]. Clinical trials to determine if combination strategies of EGFR inhibition with immune stimulating therapies may thus be superior and are warranted. Talimogene laherparepvec in combination with panitumumab could broaden the anti-tumor response by priming the locoregional microenvironment where the virus could induce pro-inflammatory cytokines and increase the expression of tumor antigens and PD-L1 by tumor cells and MHC class 1 molecules [33, 40]. This is particularly important since treatment with EGFR-inhibiting antibodies has been shown to promote EGFR-specific cellular immunity through the interaction of EGFR(+) tumor cells and FcγRIIIa on NK cells, the induction of IFN-γ-dependent expression of DC maturation markers, and the initiation of adaptive immune responses via NK cell-induced DC maturation, which enhance cross-presentation to CTL specific for EGFR [41].

1.5 Sample Size Justification

The combination of panitumumab and talimogene laherparepvec will be considered of no interest for further evaluation if the response rate in advanced SCCS is 25% (p0) or less, and considered an improved treatment if the response rate in advanced SCCS is 47% (p1) or higher. Denote the true response rate by p. Using the Simon's two-stage design [43], we will test H_0: p≤p0 vs. H_1: p>p1 with 80% power and alpha=5% (one-sided). In the first stage, 13 patients will be accrued. If there are 3 or fewer responses in these 13 patients, we will terminate the study and reject the drug (combination of panitumumab and talimogene laherparepvec). Otherwise, 17 additional patients will be accrued for **a total of 30 patients**. If 12 or more responses are observed in 30 patients, the null hypothesis will be rejected and we will conclude the success of the drug.

The combination therapy approach would be considered to have limited safety if unanticipated toxicity from talimogene laherparepvec is observed. If the proportion of talimogene-laherparepvec related grade ≥ 3 toxicities that result in hospitalization or delays/cancellation of planned surgery is less than 30% of the subjects accrued, then the study accrual may continue. These toxicities do not include fever or injection site reaction which are known side effects of talimogene laherparepvec. The toxicity will be independently monitored by the Human Research Oversight Committee which will communicate any safety concerns directly to all participating Investigators.

1.6 Study Variables

1.6.1 Independent Variables, Interventions, or Predictor Variables

The following variables will be examined for treatment outcomes of efficacy and safety, and/or predict outcomes or performance.

- Treatment
- Duration of treatment
- Baseline measures of disease
- Baseline mutation load in tumor tissue
- Baseline DNA mutation signature in tumor tissue
- Baseline mRNA signature in tumor tissue
- Baseline Immune cell populations and immune profile in tumor tissue

1.6.2 Dependent Variables or Outcome Measures

The following variables will be examined for change as a result treatment or as predictors.

- AEs
- Preliminary efficacy of the combined treatment of talimogene laherparepvec and panitumumab, in comparison to single-agent panitumumab by historical control

- irPFS at 12 months
- PFS HR
- ORR
- 1-year survival
- OS
- Time to resectability
- Pathologic complete response rate
- Response of injected and non-injected tumor deposits
- time to initial response
- durable response rate
- Change from baseline mutation load in tumor tissue
- Change from baseline DNA mutation signature in tumor tissue
- Change from baseline mRNA signature in tumor tissue
- Change from baseline Immune cell populations and immune profile in tumor tissue

1.7 Drugs/Devices/Biologics

There are no investigational agents involved in this study. Both panitumumab and talimogene laherparepvec are FDA approved drugs.

1.7.1 Pharmaceutical information (Panitumumab and Talimogene Laherparepvec):

1.7.1.1 Panitumumab

Panitumumab is a recombinant, human IgG2 kappa monoclonal antibody that binds specifically to the human EGFR.

Panitumumab Injection for Intravenous Use is manufactured by Amgen Inc., One Amgen Center Drive Thousand Oaks, CA 91320-1799.

Panitumumab Injection for Intravenous Use is a sterile, colorless, pH 5.6 to 6.0 liquid for intravenous (IV) infusion. It is available in 20 mg/mL single use vials for dosages of 100 mg/5 mL, 200 mg/10 mL or 400 mg/20 mL. Store vials in the original carton under refrigeration at 2 to 8 ˚C (36 to 46 ˚F) until time of use. Protect from direct sunlight. Do not freeze. Since panitumumab does not contain preservatives, any unused portion remaining in the vial must be discarded. The diluted infusion solution of panitumumab should be used within 6 hours of preparation if stored at room temperature or within 24 hours of dilution if stored at 2 to 8 ˚C (36 to 46 ˚F).For more information on this agent, refer to the FDA approved Package Insert.

1.7.1.2 Talimogene Laherparepvec

Talimogene laherparepvec is an oncolytic immunotherapy based on 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.

Talimogene laherparepvec is manufactured by BioVex, Inc., a subsidiary of Amgen Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799.

Talimogene laherparepvec is presented as a sterile, semi-translucent to opaque suspension, practically free from particles, and preservative free frozen liquid in a single-use 2.0 cc 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. Each 2.0 cc 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 rubber stoppers, Fluorotec-coated on the product side. The vial will be labelled with concentrations 10^6 PFU/mL or 10^8 PFU/mL.

1.7.2 Treatment Plan

1.7.2.1 General Considerations:

The experimental aspect of this protocol is in the use of panitumumab and talimogene laherparepvec in patients with locally advanced or recurrent SCCS. Panitumumab is FDA-approved for use in patients with wild-type RAS (defined as wild-type in both K-RAS and N-RAS as determined by an FDA-approved test) metastatic colorectal cancer (mCRC). The safety and optimal dosing of talimogene laherparepvec was established in melanoma [31], and it is an FDA-approved agent for metastatic melanoma.

1.7.2.2 Interim Safety Assessment and Stopping rules:

We plan to start monitoring the treatment safety after 5 patients are recruited. Monitoring will continue after every subsequent patient. The stopping rule will be determined by the posterior probability of the event rate of the either hospitalizations or delays/cancellation in planned surgery, due to treatment related toxicities. Specifically, the early stopping will be triggered when the posterior probability that more than 40% patients are either hospitalized or delayed/ cancelled in surgery due to treatment related toxicities is greater than 90%. Additional information is presented in section 6.3.2.

1.7.3 Sequence of Treatment:

1.7.3.1 Prior to Therapy

Prior to initiating therapy patients will undergo staging with history, physical and radiologic assessments to determine the extent of disease. Initial biopsy will be procedure from the primary site or regional lymph nodes. Samples will be used for confirmation of diagnosis and for molecular studies as described.

1.7.3.2 Therapy with Panitumumab and Talimogene Laherparepvec

Patients who are eligible for and consent to enroll onto this trial will receive an initial dose of 10^6 PFU/mL of talimogene laherparepvec on day 1. On day 22 patients will begin combination therapy with panitumumab at 6 mg/kg and talimogene laherparepvec at 10^8 PFU/mL, followed by this schedule every 2 weeks +/- 3 days for 3 cycles. However, dosing windows for talimogene laherparepvec are Day 22 +/- 3 days for the initial dose and +/- 3 days for any subsequent cycles. Patients will receive therapy for a total of 9 weeks prior to first restaging scans and assessment for definitive therapy. The decision may be made to offer up to 3 more cycles of therapy prior to surgery if it is felt that the tumor may continue to respond.

1.7.3.3 After Therapy with Panitumumab and Talimogene Laherparepvec

After day 64 of therapy +/- 7 days, patients will be evaluated for surgical resection. At the conclusion of treatment, we will collect peripheral blood and tumor tissue again post-treatment, either at the time of surgical resection, if applicable, or by re-biopsy. Patients will also receive a biopsy at progression, if applicable. Patients who are considered to be not candidates for definitive surgery and/or radiation therapy after the conclusion of 6 cycles, and who are benefitting from treatment with CR, PR or stable disease will be given the option to continue on protocol therapy.

1.7.4 Dose Calculations:

1.7.4.1 Panitumumab

The recommended dose of panitumumab is 6 mg/kg, administered as an intravenous infusion over 60 minutes, every 14 days. If the first infusion is tolerated, administer subsequent infusions over 30 to 60 minutes. Doses higher than 1000 mg should be administered over 90 minutes.

1.7.4.2 Talimogene Laherparepvec

The total volume of talimogene laherparepvec to be prepared will be based on investigator evaluation of injectable lesions and estimation of the total volume needed based on the Talimogene Laherparepvec Injection Volume Guideline Based on Tumor Size (Table 3). Prescribe the estimated total volume by rounding up to the nearest 1.0 mL.

The maximum volume of talimogene laherparepvec administered at any dose is 4.0 mL for any individual lesion. The maximum dose in any one treatment is 4.0 mL. Use the maximum amount whenever lesions allow.

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 3.

Table 3. Talimogene Laherparepvec Injection Volume Guideline Based on Tumor Size:

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

All reasonably injectable lesions (cutaneous, subcutaneous and nodal disease that can be injected with or without ultrasound guidance should be injected with the maximum dosing volume available on an individual dosing occasion. On each treatment day, prioritization of injections is recommended as follows:

1) Any new injectable tumor that has appeared since the last injection
2) By tumor size, beginning with the largest tumor
3) Any previously uninjectable tumor(s) that is now injectable

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

1.7.5 Treatment Administration:

1.7.5.1 Panitumumab Preparation

Prepare the solution for infusion, using aseptic technique, as follows:

1) Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Although panitumumab should be colorless, the solution may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates

(which will be removed by filtration; see below). Do not shake. Do not administer panitumumab if discoloration is observed.
2) Withdraw the necessary amount of panitumumab for a dose of 6 mg/kg.
3) Dilute to a total volume of 100 mL with 0.9% sodium chloride injection, USP. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection, USP. Do not exceed a final concentration of 10 mg/mL.
4) Mix diluted solution by gentle inversion. Do not shake.

1.7.5.2 Panitumumab Administration

Panitumumab will be administered in combination with talimogene laherparepvec on day 22 (week 3), day 36 (week 5), and to be continued on every 2 weeks thereafter.

1) Administer using a low-protein-binding 0.2 µm or 0.22 µm in-line filter.
2) Panitumumab must be administered via infusion pump.
    a) Flush line before and after panitumumab administration with 0.9% sodium chloride injection, USP, to avoid mixing with other drug products or intravenous solutions. Do not mix panitumumab with, or administer as an infusion with, other medicinal products. Do not add other medications to solutions containing panitumumab.
    b) Infuse doses of 1000 mg or lower over 60 minutes through a peripheral intravenous line or indwelling intravenous catheter. If the first infusion is tolerated, administer subsequent infusions over 30 to 60 minutes. Administer doses higher than 1000 mg over 90 minutes.
3) Use the diluted infusion solution of panitumumab within 6 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2 to 8 °C (36 to 46 °F). DO NOT FREEZE.
4) Discard any unused portion remaining in the vial.

1.7.5.3 Talimogene Laherparepvec Preparation

1) Receipt:
To ensure the stability of talimogene laherparepvec, vials must be received, unpacked and placed into storage within 90 seconds. The pharmacy team should have a plan of action to allow for quick and efficient transfer of the box of vials into the freezer (for example, by placing the shipper box close to the freezer before opening the shipper box and completing the next steps of the process).
2) Storage:
To ensure stability and quality are maintained, the product must be stored correctly upon receipt and for the duration of the study under the conditions specified below.
Talimogene laherparepvec must be stored in a non-cycling freezer maintained at a set point of -80 ºC in a secured location until planned use. Cycling, frost-free, auto defrost freezers must not be used since they cycle to warmer temperatures several times a day. Vials should be kept within the secondary container to protect from light. Table 4 below outlines the storage temperature requirements.

Table 4. Acceptable Storage Temperature:

Freezer Set Point (ºC)	Acceptable Variation	Acceptable Range
-80 °C	(± 10 °C)	-90 to -70 °C

To ensure GCP compliance with regards to the storage of biological products, talimogene laherparepvec should be segregated and stored on its own shelf in the freezer. Sites should also refer to local guidance on storing clinical trial drugs.
3) Temperature Monitoring:

Temperature monitoring of the storage temperatures, via a manual or electronic temperature log, of all locations where talimogene laherparepvec is stored is required. Actual temperature, plus range of temperatures (minimum/maximum), must be documented.
Due to the temperature sensitivity of talimogene laherparepvec, the chosen device specifications should be checked carefully to ensure the device covers the specified temperature ranges required. Temperature monitoring equipment should be serviced and calibrated in accordance with the manufacturer's guidelines and/or institutional policies.
Temperature excursions described below apply only to frozen product in storage.
4) Temperature Excursion:
A temperature excursion occurs when a Product is exposed to temperatures outside of its recommended storage range. Excursion temperature limits are defined in Table 5.

Table 5. Frozen Storage Temperature Excursion Limits:

Required Storage Temperature Range	Temperature(s) outside required storage range	Temperature excursion when the duration exceeds
-80°C ± 10°C	< -90°C (colder than -90°C)	0 minutes
	≥ -69°C to ≤ -45°C	1512 cumulative hours (63 cumulative days)
	> -45°C (warmer than -45°C)	0 minutes

For temperatures colder than -90°C and warmer than -45°C, report the excursion using the Investigator Sponsored Studies Temperature Excursion Submission Form ensuring that all details on the form are completed fully and accurately.
For temperatures within the range -69°C to -45°C, record each event within this range on the Temperature Excursion Tracking Log; cumulative duration time of the temperature excursions within this range should be captured. Once a cumulative period of 1512 hours has been reached, the site should submit the Temperature Excursion Submission Form making sure all relevant details on the form are completed fully and accurately.
Under no circumstances should any product impacted by an actual or suspected temperature excursion be administered to or by subjects before a temperature excursion assessment is completed by Amgen. Pending such an assessment, all product(s) suspected of being exposed to a temperature excursion should be quarantined under the appropriate storage conditions.
5) Reporting of temperature excursions during clinical administration is not required.
6) Talimogene laherparepvec is open-label bulk supply that can be used across study subjects.
7) Talimogene laherparepvec is supplied in two concentrations and the concentration that is to be prepared will be based on which visit the administration will occur on:
- 10^6 PFU/mL or the first dose only
- 10^8 PFU/mL for the second and all subsequent doses

8) The talimogene laherparepvec Safety Data Sheet categorizes the drug as a BioSafety Level (BSL) 1, thus use of BSL 1 containment procedures is recommended.
- The use of a microbiological safety cabinet or hood for the dispensing of talimogene laherparepvec or for dose preparation is not required for the 2.0 cc Crystal Zenith Resin stoppered vials filled with approximately 1 mL of talimogene laherparepvec that will be used in this study.
- 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.

1.7.5.4. Talimogene Laherparepvec Administration

Talimogene Laherparepvec will be administered as a single agent on day 1 (week 1), and thereafter in combination with Panitumumab on day 21 (week 3), and to be continued on weeks 5 and every 2 weeks thereafter.

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).

1) Determine which box labeled with the appropriate concentration, 10^6 PFU/mL or 10^8 PFU/mL, is to be prepared.
2) Remove the number of frozen vials from the box that have been calculated for administration. *Care should be taken to avoid unintended thawing of vials that will not be used. *Talimogene laherparepvec must be properly labeled in accordance with current ICH GCP and local/regional requirements prior to dispensing for administration. The time the vials are removed from the freezer must be recorded.
3) Thaw frozen vials until liquid at room temperature (15 °C to 30 °C or 59 °F to 86 °F). Thaw should take approximately 30 minutes. Please ensure vial is protected from light during the thaw process, using the original carton or a light protective bag (with adequate space, approximately 2.5 cm between each vial).

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

   During the thaw:
   - 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.
   - Please refer to Table 6 for the clinical handling storage times.
   - Discard materials used in the thawing (e.g. gloves) following appropriate local/regional or BSL classification guidelines.
4) 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 the 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 6 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 6: Clinical Handling Times Outside Labelled Storage Conditions

General product handling considerations	
Thaw • Thaw frozen talimogene laherparepvec vials at 15°C to 30°C (59°F to 86°F) protected from light 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.	
Total storage time for thawed 10^6 PFU/mL product	
2°C to 8°C (36°F to 46°F)	**up to 25°C (77°F)***
12 hours (inclusive of 4 hours maximum in the syringe)	4 hours (inclusive of 2 hours maximum in the syringe)
Total storage time for thawed 10^8 PFU/mL product	
2°C to 8°C (36°F to 46°F)	**up to 27°C (80°F)***
48 hours (inclusive of 8 hours maximum in the syringe)	4 hours (inclusive of 4 hours maximum in the syringe)

*This covers temperatures from 9°C to 27°C (48°F to 80°F)

5) Administration:
   - Administration of talimogene laherparepvec requires specific training which is provided during site initiation and must be completed, by individuals involved in administration, prior

to undertaking any administration related activities. Successful completion of the training must be documented.

Intralesional Administration of Talimogene Laherparepvec

- The following steps should be followed for drug administration:

Materials Inventory

- Laboratory coat, gloves and safety glasses (or as required in accordance with local/regional or BSL classification guidelines for administration)
- Dosing syringe(s) for injection filled with talimogene laherparepvec
- Sterile 22-26 gauge needle(s) for injection
- Alcohol swabs
- Absorbent pad and dry occlusive dressing

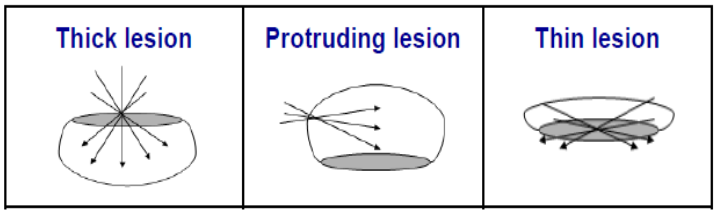
Lesion site preparation

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

Lesion injection

- All personnel handling talimogene laherparepvec or material contaminated with talimogene laherparepvec must observe safety precautions (e.g. wear a laboratory coat, safety glasses and gloves) in accordance with local/regional or BSL classification guidelines for administration).
- Inject talimogene laherparepvec intralesionally:
  - A single point of insertion is recommended; multiple insertion points may be used if the tumor is larger than the radial reach of the needle.
  - Talimogene laherparepvec should be injected along multiple different tracks within the lesion in order to obtain as wide a dispersion as possible
  - Distribute talimogene laherparepvec within the lesion through the insertion point using the radial reach of the needle in different directions to evenly distribute (Figure 3)

Figure 3. Different Tumor Lesions and Needle Insertion Points.



- Avoid premature extraction of needle.
- After dosing, the injection site should be swabbed with alcohol and pressure should be applied with gauze for several seconds after injection.

- Please ensure that gloves worn by the person administering the injection is discarded and a fresh pair of gloves is worn prior to proceeding to the next step.
- The injection site should be covered with an absorbent pad and dry occlusive dressing. Please ensure a fresh pair of gloves is worn when handling the absorbent pad and dressing to prevent cross contamination with talimogene laherparepvec. Please also ensure that the outside of the dressing is wiped down with an alcohol swab to further minimize any cross contamination.
- Discard materials used during injection (e.g., gloves, needles, gauze) in accordance with local/regional or BSL classification guidelines,

Subject Counseling Information

- Advise subjects on the potential for secondary exposure, e.g., broken skin.
- Advise subjects on careful wound care. Provide the subject with the current version of the Injection Site Care Instruction Document.
- The presence of necrotic or ulcerating lesions may predispose the subject to local and/or systemic infections such as cellulitis, bacteremia, etc. Advise subjects on careful wound care. Infection precautions are recommended if tumor necrosis results in open wounds.
- For Additional Information Related to Exposure to Talimogene Laherparepvec please refer to the latest version of your Investigator Brochure (IB) and Safety Data Sheet.

1.7.6 Dose Modifications:

Dose modifications will follow the guidelines below. In general, therapy will continue with grade 1 or tolerable grade 2 toxicities. Intolerable grade 2, grade 3, or grade 4 toxicities will result in holding therapy as follows:

1.7.6.1 Dose modification guidelines for talimogene laherparepvec:

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 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.

1.7.6.2. Talimogene Laherparepvec Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation:

If talimogene laherparepvec treatment was delayed by > 2 weeks, that dose will be deemed to have been missed and the subject will proceed to the next scheduled treatment visit. Dose reductions of talimogene laherparepvec is not permitted, other than a reduction in the volume injected due to a disease response. CTCAE 4.0 criteria listed in Table 7 are used to determine toxicity grades.

If a subject experience any of the following treatment-related toxicities, talimogene laherparepvec administration should be delayed until the toxicity has resolved to at least CTCAE grade 1 or baseline (Table 7):

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

Table 7. CTCAE 4.0 Criteria:

Symptom	Grade 1	Grade 2	Grade 3	Grade 4

Pruritis	Mild or localized	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; or constant; limiting self-care, ADLS or sleep; corticosteroid or immunosuppressive therapy indicated	N/A
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10-30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	N/A
Rash (Acneiform)	Papules and/or pustules covering <10% BSA, which may or may not be associated with pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms or pruritus or tenderness; or associated with psychosocial impact; or limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms or pruritus or tenderness; or limiting self-care ADL; or associated with local super infection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms or pruritus or tenderness and are associated with extensive super infection with IV antibiotics indicated; or life-threatening consequences
Rash (Maculo-papular)	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); or limiting instrumental ADL	Macules/papules covering >30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting self-care ADL	N/A
Nail Discoloration	Asymptomatic; or clinical or diagnostic observations only; intervention not indicated	N/A	N/A	N/A
Nail Loss	Asymptomatic	Symptomatic	N/A	N/A

	separation of nail bed from nail plate; or nail loss	separation of nail bed from nail plate; or nail loss; limiting instrumental ADL		
Nail Ridging	Asymptomatic; or clinical or diagnostic observations only; intervention not indicated	N/A	N/A	N/A

Subjects who are receiving talimogene laherparepvec may not receive systemic antiherpetic drugs (e.g., acyclovir, valacyclovir, famciclovir), but may receive a topically administered antiherpetic drug more than 20 cm from a talimogene laherparepvec injection site. Dosing should be permanently discontinued if, in the opinion of the investigator, the subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection). If the subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) for related toxicities, talimogene laherparepvec dosing must be withheld until the corticosteroid dose has decreased to < 10 mg prednisone daily (or equivalent). In clinical trials, subjects receiving systemic immunosuppressive therapy (>2 weeks) including oral steroid doses > 10 mg/day of prednisone or equivalent within 7 days prior to enrollment were excluded due to the potential risk of disseminated herpetic infection (based on animal data) in patients with immunocompromised conditions including those who require chronic high-dose steroids or other immunosuppressive agents. Thus, at this time there is no data to support use of talimogene laherparepvec in patients requiring > 10 m of prednisone.

Talimogene laherparepvec treatment should be continued based on the potential benefit/risk assessment of the subject. If talimogene laherparepvec dosing is delayed by more than 4 weeks from the date of the planned dose (i.e., approximately 6 weeks or 7 weeks depending whether the patient is receiving Q2W or Q3W dosing from the previous dose) due to the occurrence of an adverse event that is considered related to talimogene laherparepvec, the subject must be permanently withdrawn from talimogene laherparepvec treatment.
Talimogene laherparepvec is to be permanently discontinued for subjects meeting any of the following criteria:

- For phase I or Ib studies, subject develops DLT during the DLT evaluation period.
- The subject, for any reason, requires treatment with another anticancer therapeutic agent for treatment of the study disease. In this case, discontinuation from the treatment occurs immediately upon introduction of the new agent.
- Confirmed PD.
- A grade 2 or greater immune-mediated adverse event (with the exception of vitiligo) or allergic reactions attributed to talimogene laherparepvec that would require a dose delay of greater than 4 weeks from the date of the planned dose (i.e., approximately 6 weeks from the previous dose). NOTE: immune-mediated glomerulonephritis, vasculitis, and pneumonitis and exacerbation of psoriasis have been observed in subjects receiving talimogene laherparepvec in clinical trials. Most of these subjects had a history of other autoimmune disease and/or prior treatment with agents that offered plausible alternative etiologies, however, immune-mediated adverse events can potentially involve any organ system.
- Any other talimogene laherparepvec-related non-hematologic or hematologic toxicities grade 3 or greater occur that, in the opinion of the investigator, would require a dose

delay of greater than 4 weeks from the date of the planned dose (i.e., approximately 6 weeks from the previous dose).

- The subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection).
- A female subject becomes pregnant or fails to use acceptable method(s) of effective contraception (for those subjects who are able to conceive).
- A female subject breast feeds while on study treatment.
- Concurrent medical illness that, in the judgment of the investigator, would make continued treatment with talimogene laherparepvec dangerous for the subject.

For additional information related to special warnings and precautions for the use of talimogene laherparepvec, please refer to the latest version of the Investigator's Brochure.

1.7.6.3. Panitumumab

Toxicities include: Cutaneous reactions (rash, dermatitis acneiform, erythema, dry skin, pruritis, PPE), diarrhea, nausea, electrolyte disturbances (hypomagnesemia, hypocalcemia, hypokalemia), paronychia, ocular disorders, interstitial lung disease, infusion-related reactions, vomiting, constipation, abdominal pain, fatigue, pyrexia, mucositis, and anorexia.

1) Renal impairment
No clinical studies have been conducted in patients with renal impairment.

2) Hepatic impairment
No clinical studies have been conducted in patients with hepatic impairment.

3) Dose Modifications for Dermatologic Toxicity:
Withhold panitumumab for dermatologic toxicities that are grade 3 or higher or are considered intolerable. If toxicity does not improve to ≤ grade 2 within 1 month, permanently discontinue panitumumab. If dermatologic toxicity improves to ≤ grade 2, and the patient is symptomatically improved after withholding no more than two doses of panitumumab, treatment may be resumed at 50% of the original dose. If toxicities recur, permanently discontinue panitumumab (Table 8). If toxicities do not recur, subsequent doses of panitumumab may be increased by increments of 25% of the original dose until the recommended dose of 6 mg/kg is reached.

Table 8. Panitumumab dose modification for dermatologic toxicity:

Grade	Dose Modification
Grade 1	No dose modification of panitumumab
Grade 2	No dose modification of panitumumab
Grade 3/4	1st Occurrence: Delay infusion 1 to 2 weeks. If there is improvement, continue panitumumab dose at a 50% of the original dose**. If there is no improvement, discontinue panitumumab.** 2nd Occurrence: Delay infusion 1 to 2 weeks. If there is improvement, continue panitumumab dose at a 40% of the original dose. **If there is no improvement, discontinue panitumumab.** 3rd Occurrence: Delay infusion 1 to 2 weeks. If there is improvement, continue panitumumab dose at a 30% of the original dose. **If there is no improvement, discontinue panitumumab.** 4th Occurrence: **Discontinue panitumumab.**

In one study [44], dermatologic toxicities occurred in 90% of patients and were severe (grade 3 and higher) in 15% of patients receiving panitumumab. The clinical manifestations included, but were not limited to acneiform dermatitis, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and fissures. Monitor patients who develop dermatologic or soft tissue toxicities while receiving panitumumab for the development of inflammatory or infectious sequelae. Withhold or discontinue panitumumab for dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications. Patients should be advised to avoid sun exposure while receiving panitumumab.

In previous reports, the Common Terminology Criteria for Adverse Events (CTCAE) 4.0 (Table 7) have been used for EGFR-associated rash.

4) Interstitial Lung Disease (ILD)
ILD may be acute in onset and has been observed in 1.3 % of patients, and some cases have been fatal. If patients experience worsening of respiratory symptoms such as dyspnea, cough and fever, panitumumab should be interrupted and the patient should be promptly investigated. If ILD is confirmed, panitumumab should be discontinued and the patient treated appropriately.

5) Electrolyte Abnormalities
Progressively decreasing serum magnesium levels leading to severe (grade 3-4) hypomagnesemia occurred in up to 7% [45] of patients across clinical trials. Monitor patients for hypomagnesemia and hypocalcemia prior to initiating treatment with panitumumab, periodically during treatment, and for up to 8 weeks after the completion of treatment. Other electrolyte disturbances, including hypokalemia, have also been observed. Replete magnesium and other electrolytes as appropriate.

6) Infusion Reactions
In one study [44], 4% of patients receiving panitumumab experienced infusion reactions, and 1% of patients experienced severe infusion reactions (grade 3-4). Infusion reactions, manifesting as fevers, chills, dyspnea, bronchospasm, and hypotension, can occur following panitumumab administration. Table 9 and 10 show the grading criteria for infusion reactions and dose modifications for infision reactions, respectively. Fatal infusion reactions occurred in post-marketing experience.

Table 9. Grading Infusion Reactions:

	Grade 1	Grade 2	Grade 3	Grade 4
Infusion Reaction	Transient flushing or rash; drug fever <38˚C (<100 ˚F)	Rash; flushing, urticaria; dyspnea; drug fever ≥38 ˚C (≥100 ˚F)	Symptomatic bronchospasm with or without urticaria; parenteral medication(s) indicated; allergy related edema/angioedema; hypotension	Anaphylaxis

Table 10. Algorithm for Dose Modifications for Infusion Reactions:

Grade	Dose Modification
Grade 1	Stop the infusion. Consider additional anti-histamines and/or corticosteroid medications. Resume the panitumumab dose at a 50% slower rate. Consider administering prophylactic anti-histamine and corticosteroid medications and/or acetaminophen for subsequent doses.
Grade 2	Stop the infusion. Consider additional anti-histamines and/or corticosteroid medications.

	Resume the panitumumab dose at a 50% slower rate. Consider administering prophylactic anti-histamine and corticosteroid medications and/or acetaminophen for subsequent doses.
Grade 3	Stop the infusion. Administer appropriate medical therapy including epinephrine, anti-histamines, corticosteroids, bronchodilators and supplemental oxygen. Observe subject until complete resolution of all signs and symptoms. **Permanently discontinue panitumumab.**
Grade 4	Stop the infusion. Administer appropriate medical therapy including epinephrine, anti-histamines, corticosteroids, bronchodilators and supplemental oxygen. Observe subject until complete resolution of all signs and symptoms. Permanently discontinue panitumumab. **No further study therapy.**

All patients will be pre-medicated with diphenhydramine hydrochloride 50 mg (or an equivalent anti-histamine) IV 30-60 minutes prior to the first dose of panitumumab in order to prevent an infusion reaction. At the discretion of the investigator, dexamethasone 20 mg (or an equivalent steroid), and an H2 blocker may also be administered. Approximately 90% of severe infusion reactions occurred with the first infusion despite pre-medication with anti-histamines.

Once the infusion rate has been decreased due to an infusion reaction, it will remain decreased for all subsequent infusions. If the subject has a second infusion reaction at the slower infusion rate, the subject should receive no further panitumumab treatment.

Panitumumab will be immediately and permanently discontinued for serious infusion reactions that are life threatening and/or require hospitalization.

7) Photosensitivity
Exposure to sunlight can exacerbate dermatologic toxicity. Advise patients to wear sunscreen and hats and limit sun exposure while receiving panitumumab.

8) Ocular Toxicities
Keratitis and ulcerative keratitis, both known risk factors for corneal perforation, have been reported with panitumumab. Monitor for evidence of keratitis or ulcerative keratitis. Interrupt or discontinue panitumumab for acute or worsening keratitis.

9) Other Toxicities
Life-threatening and fatal infectious complications including necrotizing fasciitis, abscesses, and sepsis have been observed in patients treated with panitumumab.
Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with panitumumab.

1.7.6.4 Talimogene Laherparepvec
The most commonly reported adverse drug reactions (very common, ≥ 10%) in talimogene laherparepvec-treated patients were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain. Adverse events such as vomiting diarrhea, constipation, myalgia, arthralgia, extremity pain, headache and abdominal pain, were also reported as very common.

Dose reductions with regards to changes in the concentrations of talimogene laherparepvec are not permitted. However, patients may require a reduction in the volume injected due to a disease response or due to local toxicity at the injection site.

Dose delays are allowable. If severe/grade 4 toxicities occur, talimogene laherparepvec administration should be delayed until the toxicity has resolved to at least a grade 1. Dosing of talimogene laherparepvec could also be delayed for active herpetic cutaneous or mucosal lesions, herpes labialis, antiviral therapy, or active dermatoses in the region of the injected tumors.

If talimogene laherparepvec treatment was delayed due to adverse events or other reasons by > 2 week, that dose will be deemed to have been missed and the subject will proceed to the next scheduled treatment visit.

If talimogene laherparepvec dosing is delayed by more than 4 weeks (approximately 6 weeks from the previous dose) due to adverse events that are related to talimogene laherparepvec, then treatment should be discontinued. If talimogene laherparepvec dosing is delayed by more than 4 weeks (approximately 6 weeks from the previous dose) for reasons other than treatment-related toxicity, the case must be reviewed by the sponsor of the investigator sponsored study (ISS) to determine if the subject can resume talimogene laherparepvec therapy.

If the subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) and/or other immunosuppressive medication for related toxicities, talimogene laherparepvec dosing must be held until the corticosteroid dose has decreased to < 10 mg prednisone daily (or equivalent) and the administration of the other immunosuppressive medication has discontinued.

1) Immune-mediated Adverse Events

Immune-mediated adverse events have been observed in subjects receiving talimogene laherparepvec. These included pauci-immune glomerulonephritis, vasculitis, and pneumonitis; however, immune-mediated adverse events can potentially involve any organ system.

Permanently discontinue talimogene laherparepvec if dosing is delayed by more than 4 weeks due to a Grade 2 or greater immune-mediated adverse event (with the exception of vitiligo), allergic reactions, or urticaria attributed to talimogene laherparepvec.

2) Plasmacytoma

Plasmacytoma has been observed with the administration of talimogene laherparepvec. Permanently discontinue talimogene laherparepvec if development of a plasmacytoma is observed.

3) Injection Site Reactions

Talimogene laherparepvec is administered by direct injection into cutaneous, subcutaneous, and nodal tumor masses. Injection site adverse events may occur, such as erythema, local skin discoloration, induration, warmth, and pain. Less frequently, injected cutaneous tumor masses may undergo necrosis, predisposing the subject to local and/or systemic infections. Similarly, injected pathologic lymph nodes may enlarge or become necrotic. Uncommonly, necrotic lymph nodes may be the site of persistent drainage that requires corrective measures. In clinical studies, adverse events of “injection site pain” and “injection site reaction” were very common, occurring in ≥ 10% of talimogene laherparepvec-treated subjects. Most events of injection site pain and injection site reaction in subjects receiving talimogene laherparepvec were mild to moderate in severity. Subjects seronegative at baseline for HSV-1, when given an initial dose of talimogene laherparepvec at a concentration of 10^6 PFU/mL, do not appear to experience more exaggerated injection site reactions than those who are seropositive at baseline.

4) Cellulitis
Necrosis of cutaneous tumor masses and pathologic lymph nodes injected with talimogene laherparepvec may infrequently occur, predisposing to local/regional infection (i.e., cellulitis). In clinical studies to date, cellulitis was common, occurring in ≥ 1% to < 10% of subjects treated with talimogene laherparepvec.

5) Flu-like Symptoms
Constitutional symptoms including chills, fatigue, headache, myalgia, and pyrexia may occur with talimogene laherparepvec. Collectively, this constellation of symptoms may be described as "flu-like symptoms". In clinical studies to date, adverse events with the MedDRA preferred terms "chills", "fatigue", "headache", "influenza like illness", "myalgia", and "pyrexia" were very common, occurring in ≥ 10% of subjects treated with talimogene laherparepvec. Most of these events were mild to moderate in severity. Subjects seronegative at baseline for HSV-1, when given an initial dose of talimogene laherparepvec at a concentration of 10^6 PFU/mL, do not appear to experience more flu-like symptoms than those who are seropositive at baseline. These symptoms are self-limiting and resolve without sequelae.

1.7.7 Supportive Care Guidelines:

1.7.7.1. Panitumumab

Anti-emetics: Low emetogenicity. Follow local anti-emetic policy.
Supportive medications: Hydrocortisone, chlorphenamine and paracetamol can be given for chills/fever/rigor during the infusion, if required.

Treatment of dermatologic reactions may include a moisturizer, sun screen (SPF >15 UVA/UVB), topical steroids and/or oral antibiotics. Advise patients to wear sunscreen, a hat and limit sun exposure. Further recommendations are below:

1) Antibiotics: The benefit of routine antibiotics in uncomplicated (uninfected) rash is unclear. Some clinicians have used oral minocycline (Minocin), mupirocin (Bactroban), or topical clindamycin (Cleocin). Rash complicated by cellulitis should be treated with appropriate antibiotics based on clinical judgment or microbial sensitivity analysis.
2) Anti-histamines: Diphenhydramine (Benadryl) or hydroxyzine (Atarax) may be helpful to control itching.
3) Topical Steroids: The benefit of topical steroids is unclear. Topical hydrocortisone cream will be provided for pruritus not relieved with anti-histamine use.
4) Retinoids: There are no data to support the use of retinoids. Use is not advised.
5) Benzoyl Peroxide: Benzoyl peroxide should NOT be used as it may aggravate rash.
6) Makeup: Makeup may be used to cover the rash, but it should not make the rash worse. Dermatologist-approved make up should be used (e.g., Dermablend). Makeup should be removed with a skin-friendly liquid cleanser (e.g., Neutrogena, Dove, Ivory Skin Cleansing Liqui-Gel).
7) Moisturizers: Emollients should be used to prevent and alleviate skin dryness (e.g., Neutrogena Norwegian Formula Hand Cream, Vaseline Intensive Care Advanced Healing Lotion).
8) Over-the-Counter Medications: Over-the-counter acne vulgaris medications (e.g., benzoyl peroxide) should not be used and could make the rash worse.

1.7.7.2 Talimogene Laherparepvec

Throughout the study, investigators may prescribe supportive care medications as needed for

treatment of talimogene laherparepvec toxicities. These include but are not limited to treatment for peri-injectional fever and chills, for which antipyretics and antihistamines (i.e. acetaminophen, indomethacin and diphenhydramine) may be prescribed.

1.7.8 Important Identified and Potential Risks

1.7.8.1 Panitumumab

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

1.7.8.1 Talimogene laherparepvec

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

1.7.9 Dose-Limiting Toxicity

Dose-limiting toxicity is defined as any occurrence of CTCAE grade 3 or greater adverse event in four weeks following the administration of the study products except grade 3 laboratory values not deemed clinically significant, grade 3 fatigue which resolves within 72 h of holding or modifying protocol therapy and grade 3 rash, as the latter is an already known potential side effect of panitumumab.

1.7.9.1 **Talimogene laherparepvec DLTs**

For Talimogene laherparepvec, the following events should also be considered as DLTs.

- Herpetic events:
  - Serious herpetic events such as herpetic encephalitis, encephalomyelitis or disseminated herpetic infection.
  - Any herpetic events confirmed due to talimogene laherparepvec that 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.
- Any grade plasmacytoma at or near the injection site or evidence of impaired wound healing at the injection site.
- Grade 3 non-hematologic toxicity lasting > 3 days despite optimal supportive care;
- Grade 3 fatigue will not be classified as DLT, irrespective of duration.
- Any Grade 3 or higher non-hematologic laboratory value if the abnormality fails to respond to medical intervention, or leads to hospitalization, or persists for > 1 week unless deemed not clinically important per both investigator and sponsor.
- Any other intolerable toxicity leading to permanent discontinuation of talimogene laherparepvec.

1.7.10 Drug/Device Accountability and Storage Methods

1.7.9.1 Drug Products Storage and Security

The investigator or an approved representative (e.g., pharmacist) will ensure that all drugs and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements.

To prevent theft or diversion, the drugs will be stored in a securely locked, substantially constructed cabinet or enclosure appropriate for a drug. Any actual or suspected theft or diversion must be reported immediately.

1.7.11 Staggering Interval between the First Three Consecutive patients

The staggering interval between the first three consecutive patients will be 2 weeks past the first infusion of the combination therapy (Cycle 1,Day 21). The staggering interval of 2 weeks was based on the median time to the development of dermatologic or most severe skin/ocular toxicity of 15 days after the first dose of panitumumab (US Package Insert, panitumumab Solution for Intravenous Infusion, 2006).

1.8 Specimen Collection

1.8.1 Primary Specimen Collection

1.8.1.1 Laboratory Evaluations and Procedures/Correlative Studies: Overview of Possible Molecular Investigations:

Specimen, including tissue and blood, will be banked for the studies described below and for potential future studies. Specimens will be analyzed once funding becomes available. Samples will be transferred to NYU for analysis.

- FoundationOne™ genomic profile from paraffin embedded tumor samples taken before panitumumab and talimogene laherparepvec combination therapy, at the time of definitive surgery or biopsy, and at progression, if applicable
- mRNA sequencing by Nanostring of tumor tissue before therapy, at the time of definitive surgery or biopsy, and at progression, if applicable
- IHC analysis of immune cell populations and immune profile in peripheral blood and tumor tissue before therapy, at the time of definitive surgery or biopsy, and at progression, if applicable
- Flow cytometry analysis of immune cell populations and immune profile in peripheral blood before therapy, at the time of definitive surgery or biopsy, and at progression, if applicable

The laboratory investigations for this hypothesis generating study will be comprehensive. Partial DNA sequencing using FoundationOne™ will be done in order to look for a battery of known DNA mutations related to cancer and quantify mutation load in pre-treatment tissue, and correlate with clinical response, and examine the DNA mutation signature in tumor tissue pre- and post-therapy for biomarkers of response to therapy or resistance. FoundationOne™ is targeted DNA sequencing that is performed on paraffin embedded tumor samples. As a pan-cancer test, FoundationOne™ is designed to interrogate the entire coding sequence of 236 cancer-related genes (3,769 exons) plus 47 introns from 19 genes often rearranged or altered in cancer. These genes are known to be somatically altered in human solid cancers based on recent scientific and clinical literature.

mRNA sequencing using the Nanostring nCounter system will be done to examine the mRNA signature in tumor tissue pre- and post-therapy to identify potential future targeted strategies and to shed light on how protein production is altered when the tumor is treated with panitumumab and talimogene Laherparepvec, and correlate with clinical response for biomarkers of response to therapy or resistance. Tumors will be stored frozen in RNAlater media, and total RNA will be extracted to identify gene expression changes within the tumor and variations in immune cell populations using a CyberSort strategy. Analysis of the immune cells from the tumor will be conducted using a PanCancer Immune Profiling panel and analysis of the cancer cells from the tumor will be conducted using a PanCancer Pathways Panel provided by Nanostring. The PanCancer Immune Profiling panel profiles up to 770 gene markers of human immune responses to all cancer types, including analysis of 24 different

immune cell types and 30 common cancer antigens and genes that represent many categories of immune responses including checkpoint blockade genes (see: http://www.nanostring.com/products/pancancer_immune/). The PanCancer Pathways Panel profiles up to 770 gene markers of all major pathways, including 606 pathway genes and 124 driver genes (see: http://www.nanostring.com/products/pancancer). Once the cDNA library is created, analysis will be performed by bioinformatics.

IHC will be done to analyze immune cell populations and the immune profile on pre- and post-therapy tumor tissue, and flow cytometry will be performed on cells isolated from peripheral blood to confirm mechanism of action, and correlated with response to identify potential biomarkers of response or resistance. IHC on H&E stain will examine the immune cell infiltrate on tumor tissue, including differentiating between an influx of inflammatory cells and necrosis by way of markers of inflammation as an indicator of apoptosis. Additionally, IHC will help determine the pattern of immune cell infiltration in tumor tissue, which has been correlated with response to immunotherapy. Finally, IHC will be used to determine immune cell types both at baseline in pre-treatment, and after treatment in tumor tissue, including leukocytes (CD45+), T cells (CD3+), cytotoxic T cells (CD8+), regulatory T cells (FOXP3+), NK cells (NKP45), as well as markers of cell death by apoptosis (annexin) versus inflammation (granzyme).

Targeted flow cytometry will evaluate the frequencies, activation/differentiation, functionality, and co-inhibitory molecule expression of immune cell populations in peripheral blood before and after treatment. This will include the frequencies of T and NK cell subsets using antibodies for CD3, CD4, CD8, CD11b, CD11c, CD14, CD16, CD19, CD25, CD56, and FoxP3. Special attention will be paid to CD8 T cell:CD4Treg and NK:CD4 Treg cell ratios, with the assumption that increased effector cells (CD8 and NK cell subsets versus Treg subsets) will be an indicator of mechanism of action, and a biomarker positively associated with responsiveness to treatment. We will also examine activation and differentiation of T cell subsets using additional antibodies for HLA-DR, CD38, CD57, CCR7, CD45RA and CD45RO, with the assumption that activation and differentiation toward effector and memory responses versus exhaustion will be a biomarker positively associated with responsiveness to treatment. T cell functionality before and after treatment will be analyzed by assessing intracellular cytokine and effector molecule production using antibodies to CD107, granzyme B, IFN-γ, IL-2, and TNF-α, where increased expression will be confirmation of mechanism of action. Finally, expression of the T cell inhibitory molecules PD-1, TIM-3, 2B4, Lag-3, and CTLA-4 on $CD8^+$ T cells and their ligands (PD-L1, PD-L2, Gal9, CD48, CD80, CD86) will be evaluated on antigen presenting cells (MHC-II+) and tumor cells (CD45-) using respective monoclonal antibodies to these molecules, assuming that reduced expression of other T cell co-inhibitory molecules will both confirm mechanism of action and be a biomarker positively associated with responsiveness to treatment.

1.8.1.2 Tissue to be Collected:

All patients must have a diagnosis of SCCS prior to enrolling onto this protocol. This diagnosis is typically achieved by a biopsy from either the primary site or FNA from a locoregional lymph node. However, the scant amount of tissue obtainable from a FNA would not be adequate for the molecular biology aspects of this protocol including the pathology department for confirmation of diagnosis of SCCS, FoundationOne™ for DNA sequencing, for mRNA sequencing, and for use in IHC and flow cytometry analyses.

Thus, all patients enrolled on the protocol will have an incisional/core biopsy from the primary site prior to panitumumab and talimogene laherparepvec. Incisional biopsy is favored over other types such as core biopsy, as incisional biopsy has the best chance of supplying an adequate tumor sample.

After therapy, additional tissue will be obtained either at the time of surgery, or with a repeat biopsy if the patient is not a candidate for surgery, prior to further systemic or radiation treatment.

Additionally, all patients will have peripheral blood samples collected prior to treatment, at the time of definitive surgery or biopsy, and at the time of progression, if applicable.

1.8.1.3 Collection and Handling Procedures:
Collection and handling procedures will be performed at RWJUH, New Brunswick campus.

1) Prior to the day of the procedure, OHRS will be informed of the pending biopsies.
2) Incisional or excisional biopsy will be obtained from the primary site and BRS notified.
3) Tissues will be sent to RWJUH pathology and research specimens will be transported by BRS.
4) At RWJUH Pathology:
   A) Part of the tumor sample will be made into a paraffin embedded block; a part will be used to confirm SCCS and the remainder will be sent to FoundationOne™.
   B) Part of the tumor sample will be placed in complete media on wet ice and sent as soon as possible to the Cancer Institute Immune Monitoring Shared Resource Facility.

Samples will be transferred to NYU for analysis.

1.8.2 Secondary Specimen Collection
N/A

1.9 Data Collection

1.9.1 Primary Data Collection

Informed consent must be obtained prior to commencing any research procedures or data collection. This protocol will be available at the Rutgers Cancer Institute of New Jersey (CINJ)/Robert Wood Johnson University Hospital (RWJUH) in New Brunswick. The protocol is also currently under review at other institutions, which may participate in this study protocol.
A subset of the National Cancer Institute (NCI) CRFs, in electronic format, will be utilized. Completion of the electronic CRFs (eCRFs) will be done in accordance with the instructions in a study specific data capture plan. All eCRFs will be completed by clinical research coordinators of the OHRS. The eCRFs will be maintained in a confidential format in a secure database.
Completion of eCRFs will occur in accordance with NCI guidelines. Baseline (pre-study) eCRFs (e.g., enrollment, medical history, concomitant medications, disease assessment, etc.) will be completed no later than 14 days after the start of treatment. Treatment eCRFs (e.g., drug administration, adverse events, chemistries, etc.) will be completed no later than 14 days following each cycle of treatment. Off-treatment information (e.g., follow-up, best response, etc.) will be completed no later than 14 days after the end of protocol treatment.
A research chart (i.e., shadow chart) is maintained at OHRS for each patient enrolled. Copies of significant study source documents will be maintained in the research chart. Examples of source document copies that will be maintained in the research chart include: signed informed consent form, documents that verify eligibility and treatment, documents that verify Grade 3-4 adverse events, and response. This information will be updated on a prospective basis and will be confidentially maintained at the OHRS.
If a patient does not receive any protocol therapy, baseline data will be collected and submitted on the pre-study and follow-up electronic case report forms (eCRF). The reason for not starting protocol therapy will be documented in the “follow-up eCRF."
Case report form completion instructions and training will be provided to each participating institution prior to study activation at the participating institution.
Study evaluation parameters and the schedules of assessment are presented in the Table 1. A window of +/- 3-days is allowed for all study assessments indicated on this trial except for which otherwise indicated.

1.9.2 Secondary Data Collection
N/A

1.10 Timetable/Schedule of Events
Study evaluation parameters and the schedules of assessment are presented in the Table 1.

2.0 Project Management

2.1 Research Staff and Qualifications

2.2 Research Staff Training
The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (e.g. when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience and training to perform their specific responsibilities. These study staff members must be listed on the study centre authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.
The study monitor is responsible for explaining the protocol to all study staff, including the investigator and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

2.3 Resources Available

2.2.1 Facilities
The shared resources of Rutgers Cancer Institute of New Jersey are specialized service facilities that support the cancer research efforts of its members. The facilities include

- Advanced Microscopy
- Biomedical Informatics
- Biometrics
- Biospecimen Repository and Histopathology Service
- Immune Monitoring and Advanced Genomics
- Flow Cytometry/Cell Sorting
- Genome Editing
- Metabolomics
- Pharmacokinetics/ Pharmacodynamics
- Population Science Research Support
- Research Pharmacy

2.4 Research Sites
This protocol is available at the Rutgers Cancer Institute of New Jersey (CINJ)/Robert Wood Johnson University Hospital (RWJUH) in New Brunswick, Duke University Medical Center - Duke Cancer Center, and NYU Langone Health. The protocol is also currently under review at other institutions, which may participate in this study protocol. All biopsies and subsequent surgeries will be performed at the facilities participating in the study. Correlative studies will be performed at NYU Langone Health.

3.0 Multi-Center Research

Rutgers CINJ will coordinate and monitor the study under the direction of PI, Dr. Adam Berger, MD.

3.1 Outside Research

Please see section 2.4 and section 3.0 above.

4.0 Subject Considerations

4.1 Subject Selection and Enrollment Considerations

A. Recruitment Details

This protocol is open to both men and women, and all races.

B. Source of Subjects

Patients will be recruited from the Rutgers Cancer Institute of New Jersey, Robert Wood Johnson University Hospital, Duke University Medical Center - Duke Cancer Center, and NYU Langone Health.

C. Method to Identify Potential Subjects

A copy of the institution's IRB-approved informed consent document and written justification for any changes made to the informed consent for this protocol must be on file at the Rutgers Cancer Institute of New Jersey's Office of Human Research Services (OHRS) before any participating institution may enter patients.

To register eligible patients on this study, each site will contact OHRS. Contact information will be provided at the time of site activation. The signed and dated eligibility checklist, completed signature page of the consent form and additional source documents if requested by OHRS will need to be provided. Once OHRS verifies eligibility, the patient is considered on study. Patients must not start protocol treatment prior to enrollment.

If a patient does not receive any protocol therapy, baseline data will be collected and submitted on the pre-study and follow-up electronic case report forms (eCRF). The reason for not starting protocol therapy will be documented in the "follow-up eCRF." Case report form completion instructions and training will be provided to each participating institution prior to study activation at the participating institution.

D. Subject Screening

- **Inclusion Criteria**

A patient is eligible for enrollment if all of the following inclusion criteria are met:

1) Age 18 years or greater.
2) Histologically confirmed SCCS that is a) locally advanced or metastatic for which curative surgery or radiation would be difficult or impossible, or b) recurrent after initial surgery, chemotherapy, or radiation therapy, or c) considered to have aggressive features including the following: tumors 2 cm or more, tumors invading deep tissues such as muscle, cartilage or bone; tumors showing perineural invasion, and/or tumors metastatic to loco-regional lymph nodes. Patients may have had prior surgical interventions or been treated with investigational agents with residual or recurrent disease.
3) Tumor suitable for direct or ultrasound-guided injection defined as at least one cutaneous, subcutaneous, or nodal lesion, or aggregate of lesions, ≥ 10 mm in diameter.

4) ECOG Performance Status ≤ 2.
5) No prior treatment with panitumumab or talimogene laherparepvec for advanced disease.
6) Prior surgery or radiation is allowed if there is documented progression in the radiated/resected area or elsewhere by RECIST criteria v 1.1.
7) Measurable disease by RECIST criteria v 1.1.
8) Patients with a history of hematologic or solid organ transplant will be considered if they do not require high dose steroids or high dose immunosupressants for disease control or control of transplant rejection, and have adequate hematologic, renal, and hepatic function as specified below. Current medications must be reviewed with transplant pharmacy team to exclude potentially serious interactions and case discussed with the study PI.
9) Patients with autoimmune disorders will be considered if they do not require high dose steroids or other immunosuppressants for disease control. Prednisone in daily doses up to 10 mg and inhaled steroids are acceptable.
10) Adequate organ function is required, as defined by ALL of the following:
    a. -Absolute neutrophil count (ANC) ≥ 1500/uL
    b. -Platelet count ≥ 100,000/mm^2
    c. -Hemoglobin ≥ 9 g/dL
    d. -Total bilirubin < 1.5x institutional ULN; if patient has conditions of congenital hyperbilirubinemia, then patient must have isolated hyperbilirubinemia (e.g., no other liver function test abnormalities) with maximum bilirubin < 2x institutional ULN
    e. -AST or ALT ≤ 2.5x institutional ULN in absence of liver metastases; ≤ 5x ULN in presence of liver metastases
    f. -Alkaline phosphatase < 2.5x institutional ULN
    g. -Creatinine < 1.5x institutional ULN or calculated creatinine clearance ≥ 60 mL/min as estimated using the Cockcroft-Gault formula.

- **Exclusion Criteria**

A patient is not eligible for enrollment if any of the following exclusion criteria are met:

1) Age < 18 years.
2) Pregnant women. Women of childbearing age must be willing to undergo a pregnancy test prior to therapy and to use adequate contraception (e.g., hormonal or barrier method of contraception or abstinence) for the duration of the study and 6 months thereafter. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Menopausal status will be defined as one or more of successful hysterectomy, bilateral tubal ligation or bilateral oophorectomy, amenorrhea ≥ 12 consecutive months without another cause, or a documented serum follicle stimulating hormone (FSH) ≥ 35 mIU/mL.
3) Tumor not suitable for direct or ultrasound-guided injection.
4) Prior treatment with talimogene laherparepvec for advanced disease.
5) Second primary malignancy only if treatment would interfere with the patient's participation in this trial in the opinion of the treating physician. Clear exceptions are 1) patient had a second primary malignancy but has been treated and disease free for at least 3 years, 2) in situ carcinoma (e.g., in situ carcinoma of the cervix) and, 3) additional skin cancers that have been definitively treated by surgery and/or radiation. Patients with chronic lymphocytic leukemia will be allowed if their blood counts are within acceptable hematologic parameters and if they are not currently

requiring cytotoxic or biologic anticancer treatment (supportive treatment such as IVIG is permitted).

6) Patients with active, uncontrolled infections including active herpetic infections or chronic herpetic infections requiring anti-viral therapy (e.g., acyclovir).
7) Patients without adequate organ function as documented above.
8) History of allergic reactions attributed to compounds of similar chemical or biologic composition to panitumumab, talimogene laherparepvec or other agents used in the study.
9) History of interstitial pneumonitis, pulmonary fibrosis, or evidence of interstitial pneumonitis.

E. Recruitment Materials
N/A

4,2 Secondary Subjects
N/A

4.3 Subject Randomization
This will be a one arm Phase I study. There will be no randomization.

4.4 Secondary Subjects
N/A

4.5 Number of Subjects

4.5.1 Total Number of Subjects
This study plans to enroll 30 patients with locally advanced SCCS.

4.5.2 Total Number of Subjects If Multicenter Study
N/A

4.5.3 Require Number of Subjects to Complete Research
N/A

4.5.4 Feasibility of Recruiting
Based on past experiences with recruiting locally advanced SCCS patients at CINJ, it is expected that the intended number of 30 patients can be recruited within 12 months of this study opening.

4.6 Consent Procedures

4.6.1 Consent

4.6.1,1 Documenting Consent
Prior to study entry, the investigator, or a person designated by the investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the drugs). Sufficient time will be allowed to discuss any questions raised by the subject.

The sponsor will provide a sample informed consent form. The final version controlled form must be agreed to by the sponsor and the IRB and must contain all elements included in the sample form, in language readily understood by the subject. Each subject's original consent form,

personally signed and dated by the subject or by the subject's legally acceptable representative and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply subjects with a copy of their signed informed consent form.

The informed consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject or as a result of protocol amendments. In this instance, approval should always be given by the IRB. It is the investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as described above. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.

4.6.1.2 Waiver of Documentation of Consent

N/A

4.6.1.3 Waiver or Alteration of Consent Process

N/A

4.6.2 Consent Process

A copy of the institution's IRB-approved informed consent document and written justification for any changes made to the informed consent for this protocol must be on file at the Rutgers Cancer Institute of New Jersey's Office of Human Research Services (OHRS) before any participating institution may enter patients.

To register eligible patients on this study, each site will contact OHRS. Contact information will be provided at the time of site activation. The signed and dated eligibility checklist, completed signature page of the consent form and additional source documents if requested by OHRS will need to be provided.
The PI shall seek such consent only under such circumstances that provide the prospective patient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. The information given to the patient or the representative shall be in a language understandable to the subject or representative. The informed consent document may not include any exculpatory language through which the subject or representative is made to waive any of the subject's legal rights or releases, or appears to release the investigator, the sponsor or the institution from liability for negligence.

4.7 Special Consent/Populations

4.7.1 Minors-Subjects Who Are Not yet Adults

N/A; Children younger than 18 years of age are not eligible for this trial. SCCS is exceedingly rare in this population, and it is not expected that subjects of this age group will otherwise be eligible.

4.7.2 Non-English Speaking Subjects

It is not expected that non-English subjects will be a significant number among the 30 eligible patients. If the subject/representative cannot speak English, we will obtain the services of an interpreter fluent in both English and the language understood by the subject/representative. The interpreter may be a member of the research team, a family member, or friend of the subject/representative.
The interpreter will read the consent document or the translated consent document with the subject/representative. In addition, the interpreter will explain the details in such a way that the subject/representative understands what it would be like to take part in the research study.

4.8 Economic Burden and/or Compensation for Subjects

4.8.1 Expenses

Subjects will have tests and procedures that are part of regular medical care (not part of the research), and the subjects or the subjects' insurance company or third party provider will be responsible for these costs, including co-payments and deductibles. The doctor and other health care providers will bill the cost of regular medical care to subjects or the subjects' health insurance company in the usual way. However, some health insurance plans will not pay the costs for people taking part in studies. Subject is to check with health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular treatment. Before deciding to participate in the study, one should check with health insurance company to find out exactly what it will pay for under their policy. If the insurance does not pay for the charges of regular medical care, the sponsor will be contacted and may be able to reimburse.

Subjects will not need to pay for study drugs or tests and procedures that are done just for this research study.

If subject has any questions about insurance coverage, including any out of pocket expenses, or which laboratory or facilities you are allowed to have tests at, a financial counselor will be made available to you upon request.

4.8.2 **Compensation/Incentives**

Subjects will not be compensated for participation in this research study.

4.9 Risks of Harm/Potetial for Benefits to Subjects

4.9.1 Potential Risks:

Potential risks to the patient, secondary to panitumumab, include hypersensitivity reaction, rash, thrombosis, hypomagnesemia, hypocalcemia and pulmonary complications. Potential risks to the patient, secondary to talimogene laherparepvec, include fever, flu-like illness and injection site reactions. These will be monitored as detailed in the adverse events section. In terms of the individual's cancer, there is a risk of the treatment being ineffective, and by extension, the possibility of disease progression.

4.9.2 Consent Procedures:

Because of the above potential risks, informed consent must be obtained prior to commencing any research procedures. The PI shall seek such consent only under such circumstances that provide the prospective patient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. The information given to the patient or the representative shall be in a language understandable to the subject or representative. The informed consent document may not include any exculpatory language through which the subject or representative is made to waive any of the subject's legal rights or releases, or appears to release the investigator, the sponsor or the institution from liability for negligence.

4.9.3 Potential Benefits:

The benefits of participating in this study may be improvement in a patient's cancer either as a measure of disease activity or quality of life improvements.

4.9.4 Risk-Benefit Ratio:

All risks and benefits of this treatment will be discussed with the patient prior to enrollment on this study. Along these lines, the basic principles of what we are hoping to accomplish with the combination of panitumumab and talimogene laherparepvec followed by surgery will be explained. The potential risks detailed in Section 4.9.1 will be made clear as well, along with what measures are in place to minimize these risks.

Alternative treatment will also be discussed. These options include beginning standard chemotherapy if applicable, anti-EGFR monoclonal antibody monotherapy, monitoring off therapy, or enrolling in another clinical trial. Additionally, the importance of the knowledge gained through this study will be discussed with the patient.

All told, with the combination of employing proper patient selection and study termination criteria, close clinical and lab follow-up (both of the cancer as well as other relevant body systems), and the medical knowledge of panitumumab and talimogene laherparepvec (as FDA-approved medications for oncologic medical purposes in head and neck cancer, colon cancer and melanoma), we believe the potential benefits outweigh the risks of the trial.

4.10 Secondary Data – Records/Chart Reviews/Databases/Tissue Banks/etc.
N/A

4.11 Chart/Record Review Selection

In compliance with GCP guidelines, the medical records/medical notes, etc., should be clearly marked and permit easy identification of a subject's participation in the specified clinical study.

The investigator/authorized staff must record all data relating to protocol procedures, drug administration, laboratory data, safety data and efficacy ratings on the CRFs/eCRFs provided for the study. The investigator, by completing the signature log, may formally designate authority to complete CRFs/eCRFs to appropriately qualified staff. Any data management queries and items not adequately explained will be returned to the investigator by the monitor for clarification/correction. The investigator must ensure that data queries are dealt with promptly. Copies of all data changes and clarifications must be retained by the investigator and filed with the CRFs.

The investigator must, as a minimum, provide an electronic signature (e-signature) to each case report book to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF after a form has been locked and electronically signed, the investigator will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and a reason for change is always required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

If requested, the investigator will provide the sponsor, applicable regulatory agencies and applicable EC with direct access to any original source documents.

4.12 Secondary Specimen Collection
N/A

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)
N/A

5.2 Family Educational Rights and Privacy Act (FERPA)
N/A

5.3 NJ Access to Medical Research Act
N/A

5.4 General Data Protection Regulation (GDPR)
N/A

5.5 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)
N/A

6.0 Data Management Plan

6.1 Data Analysis

6.1.1 Statistical Considerations

This is a pilot feasibility study that will assess the safety and preliminary efficacy of this approach. As a phase I trial, safety of the combination will be assessed and the study stopped early for subject safety according to stopping rules defined in section 6.3.2 below. A two-stage design often used for phase II studies will be applied with the objective of estimating response rate as a measure of efficacy.

Descriptive statistics for all outcome measures and patient characteristics will be provided. The response rate of the drug will be assessed according to the decision rule based on Simon's Two-Stage Design outlined in the Sample Size Justification Section. As a secondary outcome, the pCR will be calculated and reported with its 95%confidence interval. The estimation of progression-free survival (PFS) and overall survival (OS) will be performed by the Kaplan-Meier product limit method. Logrank test and Cox proportional hazards model will be used to explore the associations between outcome measures (PFS and OS) and patient characteristics.

6.1.2 Interim Safety Assessment and Stopping rules

We will employ a 3 + 3 study design in the first six patients enrolled. This will allow for early detection of unexpected safety signals and will allow for rapid implementation of measures to diminish the risk of toxicity to subsequently enrolled subjects. The interim safety assessment will start and includes the rules of the 3+3 design based on the incidence of DLTs. We plan to continue monitoring the treatment safety after the first 6 patients are recruited. Monitoring will continue after every subsequent patient. The stopping rule will be determined by the posterior probability of the event rate of the either hospitalizations or delays/cancellation in planned surgery, due to treatment related toxicities. Specifically, the early stopping will be triggered when the posterior probability that more than 40% patients are either hospitalized or delayed/ cancelled in surgery due to treatment related toxicities is greater than 90%. Assuming a non-informative prior, we calculated the posterior probability of toxicity related event rate of 40% given that k events are observed out of the first n patients, using the beta distribution with shape parameter 1+k and scale parameter 1+n-k. Table 10 highlights the posterior probability that more than 40% patients are either hospitalized or delayed/cancelled in surgery due to treatment related toxicities being greater than 90%. If 6 or more toxicity related events that meet these criteria of resulting in hospitalization or delays/cancellation of planned surgery out of the first 10 patients are observed, the trial will be stopped.

Note that each cell of Table 11 contains the posterior probability that the true toxicity related event rate is greater than 40% given that k events are observed out of the first n patients. The prior distribution will be updated based on the number of events observed at each monitoring, and thus resulting posterior

probability of the event rate greater than 40% will also be updated. The study PI (Dr. Berger) then will contact the Biometrics division at the Rutgers Cancer Institute of New Jersey to obtain the updated stopping rule after each scheduled monitoring.

Table 11. Posterior probability of toxicity related event rate of 40% given that k events are observed out of the first n patients

	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
5	0.821	0.959	0.996	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
6	0.710	0.904	0.981	0.998	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
7	0.594	0.826	0.950	0.991	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
8	0.483	0.733	0.901	0.975	0.996	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
9	0.382	0.633	0.834	0.945	0.988	0.998	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
10	0.296	0.533	0.753	0.901	0.971	0.994	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
11	0.225	0.438	0.665	0.842	0.943	0.985	0.997	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
12	0.169	0.353	0.574	0.771	0.902	0.968	0.992	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
13	0.124	0.279	0.486	0.692	0.850	0.942	0.982	0.996	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
14	0.091	0.217	0.403	0.610	0.787	0.905	0.966	0.991	0.998	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
15	0.065	0.167	0.329	0.527	0.716	0.858	0.942	0.981	0.995	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000
16	0.046	0.126	0.264	0.448	0.641	0.801	0.908	0.965	0.989	0.997	1.000	1.000	1.000	1.000	1.000	1.000	1.000
17	0.033	0.094	0.209	0.374	0.563	0.737	0.865	0.942	0.980	0.994	0.999	1.000	1.000	1.000	1.000	1.000	1.000
18	0.023	0.070	0.163	0.308	0.488	0.667	0.814	0.912	0.965	0.988	0.997	0.999	1.000	1.000	1.000	1.000	1.000
19	0.016	0.051	0.126	0.250	0.416	0.596	0.755	0.872	0.943	0.979	0.994	0.998	1.000	1.000	1.000	1.000	1.000
20	0.011	0.037	0.096	0.200	0.350	0.524	0.691	0.826	0.915	0.965	0.988	0.996	0.999	1.000	1.000	1.000	1.000
21	0.008	0.027	0.072	0.158	0.290	0.454	0.624	0.772	0.879	0.945	0.979	0.993	0.998	1.000	1.000	1.000	1.000
22	0.005	0.019	0.054	0.124	0.237	0.388	0.556	0.713	0.836	0.919	0.965	0.987	0.996	0.999	1.000	1.000	1.000
23	0.004	0.013	0.040	0.096	0.192	0.328	0.489	0.650	0.787	0.886	0.947	0.978	0.992	0.998	0.999	1.000	1.000
24	0.002	0.009	0.029	0.074	0.154	0.274	0.425	0.586	0.732	0.846	0.922	0.966	0.987	0.996	0.999	1.000	1.000
25	0.002	0.007	0.021	0.056	0.122	0.226	0.364	0.521	0.674	0.801	0.892	0.948	0.978	0.992	0.998	0.999	1.000
26	0.001	0.005	0.015	0.042	0.095	0.184	0.309	0.458	0.613	0.750	0.855	0.926	0.966	0.987	0.995	0.999	1.000
27	0.001	0.003	0.011	0.031	0.074	0.148	0.259	0.399	0.551	0.695	0.813	0.898	0.950	0.978	0.992	0.997	0.999
28	0.000	0.002	0.008	0.023	0.057	0.119	0.215	0.343	0.490	0.637	0.766	0.864	0.929	0.967	0.987	0.995	0.998
29	0.000	0.002	0.006	0.017	0.044	0.094	0.176	0.291	0.431	0.578	0.715	0.825	0.903	0.952	0.979	0.992	0.997

6.1.3 Preliminary Efficacy Assessment

6.1.3.1 Primary Hypothesis:

For efficacy, we hypothesize that the combination of panitumumab and talimogene laherparepvec will improve the response rate in advanced SCCS from 25% with single agent panitumumab [1] to 47% (near doubling of response rate to justify added expense and time required for administration of second drug as well as potential for additional toxicities).

6.1.3.2 Sample Size Justification and Stopping Rules:
A detailed analysis for sample size justification is presented in Section 1.5.

The combination therapy approach would be considered to have limited safety if unanticipated toxicity from talimogene laherparepvec is observed. If the proportion of talimogene-laherparepvec related grade ≥ 3 toxicities that result in hospitalization or delays/cancellation of planned surgery is less than 30% of the subjects accrued, then the study accrual may continue. These toxicities do not include fever or injection site reaction which are known side effects of talimogene laherparepvec. The toxicity will be independently monitored by the Human Research Oversight Committee which will communicate any safety concerns directly to all participating Investigators.

6.1.3.3 Secondary endpoints to be captured include:

- To assess the clinical efficacy of panitumumab in combination with intratumoral talimogene laherparepvec in terms of immune-related progression-free survival (irPFS)at 12 months, overall response rate (ORR), 1-year survival, overall survival (OS) and time to resectability.
- To measure the pathologic complete response rate to panitumumab combined with talimogene laherparepvec.
- Assess the response of injected and non-injected tumor deposits after panitumumab and talimogene laherparepvec.
- Assess the time to initial response.
- Assess the durable response rate.
- To analyze the following molecular correlate with response to therapy to confirm mechanism of action, and identify potential future targeted strategies and biomarkers of response:
    A) Mutation load in tumor tissue by next generation sequencing
    B) DNA mutation signature in tumor tissue pre- and post-therapy by next generation sequencing
    C) mRNA signature in tumor tissue pre-and post-therapy by Nanostring technology

    D) Immune cell populations and immune profile in pre- and post-therapy tumor tissue and peripheral blood by flow cytometry and IHC

6.1.4 Outcome Measures:
All efficacy analysis will be based on the intention to treat population, which will include all enrolled patients. The primary outcome is the response rate to combination treatment with panitumumab and talimogene laherparepvec by RECIST 1.1 criteria in patients with advanced SCCS.
Secondary outcomes include best overall response rate, durable response rate and duration of response, progression free survival, overall survival in patients who receive panitumumab and talimogene laherparepvec. Molecular correlates will also be obtained and descriptive statistics applied.

PFS is defined as the number of months from the date of enrollment to the date of death or progression, whichever occurred earlier (per RECIST 1.1). If neither death nor progression is observed during the study, PFS data will be censored at the last valid tumor assessment. If patient is rendered disease free from surgical removal of tumor (section 1.3.2), progression is determined to be the date of diagnosis of recurrence.
Overall survival is defined as the time from the date of patient enrollment to date of death or the date last known alive.
Best Overall Response Rate (ORR) is defined as the best response as recorded from the start of study drug until disease progression. Patients without a post-baseline tumor assessment will be considered to be non-evaluable for best ORR. To classify best ORR as stable disease (SD), there should be a qualifying SD assessment at least 6 weeks from enrollment. Overall Response Rate (ORR) is defined as the proportion

of patients with a best ORR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Only patients with measurable disease at baseline will be included in the analysis of the objective response.
Durable response rate is defined as the percent of patients with complete response or partial response maintained continuously for a minimum of 6 months. Response duration is defined as the time from initial response until documented progression.
For subjects converted to resectable and surgical resection is performed (complete or partial), response endpoints will be censored at the time of surgery. However, these patients will still be followed for PFS and OS.

6.1.5 Toxicity Monitoring and Adverse Event Reporting:
All patients who receive one dose of protocol therapy will be evaluable for assessment of toxicity. Prior to each cycle, the treating physician will fully assess the patient's condition with respect to possible treatment related toxicities. All adverse events, whether observed by the physician or reported by the patient, occurring during the active portion of therapy, or up to 30 days after the last dose of treatment will be graded by a numerical score according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (see http://ctep.cancer.gov/reporting/ctc.html) and recorded in the patient's medical record. For the purposes of reporting laboratory abnormalities, only Grade 3-4 adverse events will be recorded on the adverse event CRF pages. Grade 1-2 laboratory abnormalities will not be recorded on the adverse event CRF pages. Information entered on the adverse event CRF pages will include:

6) Specific type and duration of reaction (i.e., start and stop dates, resolution)
7) Severity/grade
8) Relationship to study drug (causality, attribution)
9) Management of the event, if treated with medication and other actions taken to alleviate the clinical event
10) Whether or not it was considered a SAE

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

6.1.5.1. Adverse Event Reporting Requirements:
An adverse experience is defined as any unintended or abnormal clinical observation that is not of benefit to the patient. Either the condition was not present prior to exposure to the study therapy, or it has worsened in intensity or frequency following exposure to the study therapy.

All "unexpected" (defined below) and/or "serious" (defined below) adverse events occurring during the active portion of therapy, or up to 30 days after the last dose of treatment, will be reported to the OHRS at (732) 235-7577 or (732) 235-8675. Events will be promptly reported, in writing, to the local IRB in accordance with IRB policy. If a death or a life-threatening event occurs, the IRB will be notified within 24-hours of initial receipt of information. All other SAEs must be reported to the IRB within three to ten days of initial receipt of information. Written follow-up reports are required when additional information is needed to fully characterize the event. Copies of each report sent to the IRB will be kept in the study regulatory file.

In addition to reporting to the local IRB, reporting to external bodies such as industry and/or the FDA may be necessary. The Oncology group affiliates site will report all SAEs to the OHRS and will also be responsible for forwarding SAE reports to the IRB and FDA. In addition, information included in the SAE form will be provided to the PI/sponsor or its representative as soon as it is available. Moreover, an SAE line-listing will be sent to the PI/sponsor at least every 6 months.

6.1.5.2 Reporting SAEs using commercially available drugs:
The PI shall notify the FDA of any adverse experience related to the use of Talimogene Laherparepvec and Panitumumab combination that is both serious and unexpected, as soon as possible and in no event later than 15 calendar days after the PI's discovery of the event. Each written notification may be submitted on FDA Form MedWatch 3500A http://www.fda.gov/medwatch/safety/3500a.pdf (fax # 1-800-FDA-0178). The PI shall also notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experiences associated with the use of Talimogene Laherparepvec and Panitumumab combination, as soon as possible but no later than 7 calendar days from the PI's discovery of the event information.

6.1.5.3 Safety Reporting to Amgen
The Sponsor/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 12 and Table 13 below. Individual safety reports (Table 12) should be accompanied by the Fax Cover Form provided in Appendix 1, and sent to Amgen Global Safety, utilizing the fax or email information provided on the cover page. Aggregate safety reporting (Table 13) including listings, tabulations and summary reports should be scanned and accompanied by the Fax Cover Form provided in Appendix 2, and sent to Amgen NASCR, utilizing the email information provided on the cover page. In addition to the requirements outlined in Table 12 and 13, Sponsor/Investigators are required to report direct exposures to talimogene laherparepvec (e.g., needle stick, splash back) of herpetic illness and all suspected herpetic events (refer to Section 6.3.6.4, 'Accidental Exposures to Talimogene Laherparepvec and Herpetic Events').

Table 12. Expedited Reporting Requirements for Interventional Studies:

Safety Data	Time frame 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 4 and Appendix 5 for Amgen template forms)

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

Table 13. Aggregate Reports:

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

Aggregate reports should be submitted by email to the Amgen NASCR manager, accompanied by the Fax Cover Form shown in Appendix 2.

Please refer to the ICH Guidelines E2A for safety related definitions and terminology: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideli ne.pdf.

6.1.5.4 Accidental Exposures to Talimogene Laherparepvec 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 14 for a summary of reporting requirements. Clinicians should review the Imlygic package insert (available online) for additional information on the safe handling of talimogene laherparepvec.

Table 14. Accidental Exposure & Herpetic Event Reporting Requirement Summary:

Exposed Person	Reporter	Timeframe for Reporting to Amgen	Report Mechanism	Timing of Swab Collection	qPCR Testing ?	Responsible Party for Lesion Swabbing	qPCR Test Result Distribution*
Treated Patients **with suspected herpetic lesions**	Sponsor / Investigator	Within 24 hours of Sponsor / Investigator awareness	Contact Amgen at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions (ideally within 3 days of appearance of symptoms)	Yes, if consent obtained	Sponsor / Investigator	Sponsor / Investigator and Amgen
HCP directly exposed to product (e.g., needle stick, splash back) without signs or	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	N/A	N/A	N/A	N/A

symptoms of herpetic illness			event				
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 (e.g. caregiver, spouse, child) **with suspected herpetic lesions**	Sponsor / Investigator, Close Contact's Personal Physician or Close Contact	Within 24 hours of Reporter awareness	Contact Amgen at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions (ideally within 3 days of appearance of symptoms)	Yes, if consent obtained	Sponsor / Investigator, Close Contact's Personal Physician	Sponsor / Investigator, Close Contact's Personal Physician and Amgen

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

6.1.5.5 Accidental Exposure of HCPs to Talimogene Laherparepvec

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

6.1.5.6 Suspected Herpetic Events

Suspected herpetic events must be reported to Amgen within 24 hours of awareness. Reporting is required for: (1) suspected herpetic events in treated patients; (2) suspected herpetic events in at risk HCPs with direct or indirect exposure and 3) suspected herpetic events in treated patient's close contacts, as outlined in Table 13. An example of the Suspected IMLYGIC™ (Talimogene laherparepvec) or Herpes Virus Associated Adverse Event can be found in Appendix 3.

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

6.1.5.7 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.

6.1.5.8 Reporting Process for HCPs and Close Contacts:

Sponsor/Investigator should advise any HCPs and/or Close Contacts with suspected herpetic

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

6.1.6 Definition of Serious Adverse Events:

A serious adverse event (experience) is one that results in any of the following outcomes:

1) Death
2) Threat to life (immediate risk of death from the reaction)
3) Inpatient hospitalization or prolongation of existing hospitalization
4) Persistent or significant disability/incapacity
5) Congenital anomaly/birth defect
6) Intervention required to prevent one of the above outcomes listed in this definition

The definition of serious adverse event (experience) also includes *important medical events*. Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events will usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

6.1.6.1 Definition of Related:

There is a reasonable possibility that the drug caused the adverse experience. That is, the event is judged by the investigator to be possibly, probably or definitely related to the treatment.

6.1.6.2 Definition of Unexpected:

Any adverse drug experience and/or specificity, that is not included in the current investigator's brochure and/or package insert.

6.1.7 Removal of Patients from Study/Off Study Criteria

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

a) Intercurrent illness of SAE that prevents further administration of treatment,
b) Patient decides to withdraw from the study,
c) Noncompliance with treatment plan,
d) General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,
e) Protocol violation - any patient found to have entered this study in violation of the protocol might be discontinued from the study at the discretion of the Principal Investigator.

6.2 Data Security

Wherever feasible, Electronic Data Capture (EDC) will be utilized for collecting subject data. All study personnel are required to have a computer and internet connection available for entry of clinical data. All entries in the eCRF will be made under the e-signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. Only PI/Investigator authorized users will have access to the eCRF as appropriate to their study

responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.
For non EDC elements, the PI will ensure that appropriate data entry methods are used (e.g. double data entry) and suitable queries are raised to resolve any missing or inconsistent data.

6.2.1 Case Report Forms:
A subset of the National Cancer Institute (NCI) CRFs, in electronic format, will be utilized. Completion of the electronic CRFs (eCRFs) will be done in accordance with the instructions in a study specific data capture plan. All eCRFs will be completed by clinical research coordinators of the OHRS. The eCRFs will be maintained in a confidential format in a secure database.

6.2.2 Data Submission Timeline and Forms:
Completion of eCRFs will occur in accordance with NCI guidelines. Baseline (pre-study) eCRFs (e.g., enrollment, medical history, concomitant medications, disease assessment, etc.) will be completed no later than 14 days after the start of treatment. Treatment eCRFs (e.g., drug administration, adverse events, chemistries, etc.) will be completed no later than 14 days following each cycle of treatment. Off-treatment information (e.g., follow-up, best response, etc.) will be completed no later than 14 days after the end of protocol treatment.

6.2.3 Research Charts:
A research chart (i.e., shadow chart) is maintained at OHRS for each patient enrolled. Copies of significant study source documents will be maintained in the research chart. Examples of source document copies that will be maintained in the research chart include: signed informed consent form, documents that verify eligibility and treatment, documents that verify Grade 3-4 adverse events, and response. This information will be updated on a prospective basis and will be confidentially maintained at the OHRS.

6.2.4 Reports:
Publications and annual reports for submission to the IRB will be written by the Rutgers Cancer Institute of New Jersey PI using the data captured on the e-CRFs. Results will be communicated at scientific meetings and all reasonable efforts must be made to seek publication in a peer-reviewed scientific journal.

6.3 Data and Safety Monitoring
Monitoring of this study will occur in accordance with the Cancer Institute's NCI approved Data and Safety Monitoring Plan (DSMP). An "initiation audit" will be conducted in accordance with the DSMP following enrollment of the first two (2) or three (3) patients. Subsequent audits will occur on an annual basis prior to annual IRB continuing review, if the findings from the initiation audit were satisfactory. More frequent audits of patient data and study conduct will occur if necessary. Prior audit findings and/or situations that may arise during the course of the study will determine the need for more frequent auditing. All audit findings will be reported to the Cancer Institute's Human Research Oversight Committee and the PI.

6.4 Reporting Results

A. Sharing of Results with Subjects
N/A

B. Individual Results
N/A

C. Aggregate Results
N/A

6.4.1 Professional Reporting
Results will be communicated at scientific meetings and all reasonable efforts will be made to seek publication in a peer-reviewed scientific journal.

6.4.2 ClinicalTrials.Gov Registration and Data Reporting

The study will be be registered by the PI with https://orra.rutgers.edu/clinicaltrialsgov. Summary of the study results will be posted to the CTG site as and when available.

6.5 Data Sharing

After information that could identify patients (PHI) has been removed, de-identified information or biospecimens collected for this research may be used by or distributed to investigators for other research.

6.6 Secondary Use of the Data

After information that could identify identify patients (PHI) has been removed, de-identified information collected for this research may be used by or distributed to investigators for other research.

7.0 Research Repositories – Specimens and/or Data

Your leftover tissue samples will be stored in the Cancer Institute of New Jersey Biorepository Service (BRS), which is owned and operated by the Rutgers Cancer Institute of New Jersey. The repository is at 195 Little Albany Street, New Brunswick, NJ, 08903 and operates through BRS SOPs (IRB 0220100249/CINJ protocol 001006).

8.0 Approvals/Authorizations

N/A

9.0 Bibliography

1. Foote, M.C., et al., *Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma.* Ann Oncol, 2014. **25**(10): p. 2047-52.
2. Karia, P.S., et al., *Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma.* J Clin Oncol, 2014. **32**(4): p. 327-34.
3. Karia, P.S., J. Han, and C.D. Schmults, *Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012.* J Am Acad Dermatol, 2013. **68**(6): p. 957-66.
4. Hacker, S.M. and F.P. Flowers, *Squamous cell carcinoma of the skin. Will heightened awareness of risk factors slow its increase?* Postgrad Med, 1993. **93**(8): p. 115-21, 125-6.
5. Marks, R., *The epidemiology of non-melanoma skin cancer: who, why and what can we do about it.* J Dermatol, 1995. **22**(11): p. 853-7.
6. Alam, M. and D. Ratner, *Cutaneous squamous-cell carcinoma.* N Engl J Med, 2001. **344**(13): p. 975-83.
7. Clayman, G.L., et al., *Mortality risk from squamous cell skin cancer.* J Clin Oncol, 2005. **23**(4): p. 759-65.
8. Navarrete-Dechent, C., et al., *High-risk cutaneous squamous cell carcinoma and the emerging role of sentinel lymph node biopsy: A literature review.* J Am Acad Dermatol, 2015. **73**(1): p. 127-37.
9. Parikh, S.A., V.A. Patel, and D. Ratner, *Advances in the management of cutaneous squamous cell carcinoma.* F1000Prime Rep, 2014. **6**: p. 70.
10. Oddone, N., et al., *Metastatic cutaneous squamous cell carcinoma of the head and neck: the Immunosuppression, Treatment, Extranodal spread, and Margin status (ITEM) prognostic score to predict outcome and the need to improve survival.* Cancer, 2009. **115**(9): p. 1883-91.
11. Veness, M.J., *Treatment recommendations in patients diagnosed with high-risk cutaneous squamous cell carcinoma.* Australas Radiol, 2005. **49**(5): p. 365-76.
12. Cartei, G., et al., *Oral 5-fluorouracil in squamous cell carcinoma of the skin in the aged.* Am J Clin Oncol, 2000. **23**(2): p. 181-4.
13. Ikegawa, S., et al., *Cisplatin combination chemotherapy in squamous cell carcinoma and adenoid cystic carcinoma of the skin.* J Dermatol, 1989. **16**(3): p. 227-30.
14. Jarkowski, A., 3rd, et al., *Systemic Therapy in Advanced Cutaneous Squamous Cell Carcinoma (CSCC): The Roswell Park Experience and a Review of the Literature.* Am J Clin Oncol, 2014.
15. Guthrie, T.H., Jr., et al., *Cisplatin-based chemotherapy in advanced basal and squamous cell carcinomas of the skin: results in 28 patients including 13 patients receiving multimodality therapy.* J Clin Oncol, 1990. **8**(2): p. 342-6.
16. Sadek, H., et al., *Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin.* Cancer, 1990. **66**(8): p. 1692-6.
17. Shin, D.M., et al., *Phase II and biologic study of interferon alfa, retinoic acid, and cisplatin in advanced squamous skin cancer.* J Clin Oncol, 2002. **20**(2): p. 364-70.
18. Snyder, A., et al., *Genetic basis for clinical response to CTLA-4 blockade in melanoma.* N Engl J Med, 2014. **371**(23): p. 2189-99.
19. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.
20. Hodi, F.S., et al., *Evaluation of Immune-Related Response Criteria and RECIST v1.1 in Patients With Advanced Melanoma Treated With Pembrolizumab.* J Clin Oncol, 2016. **34**(13): p. 1510-7.
21. Gaffney, D.C., H.P. Soyer, and F. Simpson, *The epidermal growth factor receptor in squamous cell carcinoma: An emerging drug target.* Australas J Dermatol, 2014. **55**(1): p. 24-34.

22. Maubec, E., et al., *Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin.* J Clin Oncol, 2011. **29**(25): p. 3419-26.
23. Kim, S., M. Eleff, and N. Nicolaou, *Cetuximab as primary treatment for cutaneous squamous cell carcinoma to the neck.* Head Neck, 2011. **33**(2): p. 286-8.
24. Lopez-Albaitero, A. and R.L. Ferris, *Immune activation by epidermal growth factor receptor specific monoclonal antibody therapy for head and neck cancer.* Arch Otolaryngol Head Neck Surg, 2007. **133**(12): p. 1277-81.
25. Pajares, B., et al., *Differential outcome of concurrent radiotherapy plus epidermal growth factor receptor inhibitors versus radiotherapy plus cisplatin in patients with human papillomavirus-related head and neck cancer.* BMC Cancer, 2013. **13**: p. 26.
26. Vermorken, J., et al., *Safety and Efficacy of Panitumumab (pmab) in HPV Positive (+) and HPV Negative (−) Recurrent/metastatic (R/M) Squamous Cell Carcinoma of the Head and Neck (SCCHN): Analysis of the Phase 3 SPECTRUM Trial.* European Journal of Cancer. **47**: p. 13.
27. Vermorken, J.B., et al., *Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial.* Lancet Oncol, 2013. **14**(8): p. 697-710.
28. Wirth, L.J., et al., *Phase I dose-finding study of paclitaxel with panitumumab, carboplatin and intensity-modulated radiotherapy in patients with locally advanced squamous cell cancer of the head and neck.* Ann Oncol, 2010. **21**(2): p. 342-7.
29. National Comprehensive Cancer, N., *Squamous Cell Skin Cancer (Version 1.2015).* 2014.
30. Mavropoulos, J.C., B. Aldabagh, and S.T. Arron, *Prospects for personalized targeted therapies for cutaneous squamous cell carcinoma.* Semin Cutan Med Surg, 2014. **33**(2): p. 72-5.
31. Andtbacka, R.H., et al., *Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma.* J Clin Oncol, 2015. **33**(25): p. 2780-8.
32. Johnson, D.B., I. Puzanov, and M.C. Kelley, *Talimogene laherparepvec (T-VEC) for the treatment of advanced melanoma.* Immunotherapy, 2015. **7**(6): p. 611-9.
33. Dharmadhikari, N., J.M. Mehnert, and H.L. Kaufman, *Oncolytic virus immunotherapy for melanoma.* Curr Treat Options Oncol, 2015. **16**(3): p. 326.
34. Taneja, S., et al., *Enhanced antitumor efficacy of a herpes simplex virus mutant isolated by genetic selection in cancer cells.* Proc Natl Acad Sci U S A, 2001. **98**(15): p. 8804-8.
35. Hu, J.C., et al., *A phase I study of OncoVEXGM-CSF, a second-generation oncolytic herpes simplex virus expressing granulocyte macrophage colony-stimulating factor.* Clin Cancer Res, 2006. **12**(22): p. 6737-47.
36. Senzer, N.N., et al., *Phase II clinical trial of a granulocyte-macrophage colony-stimulating factor-encoding, second-generation oncolytic herpesvirus in patients with unresectable metastatic melanoma.* J Clin Oncol, 2009. **27**(34): p. 5763-71.
37. Xia, Z.J., et al., *[Phase III randomized clinical trial of intratumoral injection of E1B gene-deleted adenovirus (H101) combined with cisplatin-based chemotherapy in treating squamous cell cancer of head and neck or esophagus].* Ai Zheng, 2004. **23**(12): p. 1666-70.
38. Varghese, S. and S.D. Rabkin, *Oncolytic herpes simplex virus vectors for cancer virotherapy.* Cancer Gene Ther, 2002. **9**(12): p. 967-78.
39. Chung, C.H., et al., *Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas.* J Clin Oncol, 2006. **24**(25): p. 4170-6.
40. Spranger, S., et al., *Up-regulation of PD-L1, IDO, and T(regs) in the melanoma tumor microenvironment is driven by CD8(+) T cells.* Sci Transl Med, 2013. **5**(200): p. 200ra116.
41. Srivastava, R.M., et al., *Cetuximab-activated natural killer and dendritic cells collaborate to trigger tumor antigen-specific T-cell immunity in head and neck cancer patients.* Clin Cancer Res, 2013. **19**(7): p. 1858-72.
42. Trivedi, S., et al., *Immune biomarkers of anti-EGFR monoclonal antibody therapy.* Ann Oncol, 2015. **26**(1): p. 40-7.

43. Simon, R., *Optimal two-stage designs for phase II clinical trials.* Control Clin Trials, 1989. **10**(1): p. 1-10.
44. Van Cutsem, E., et al., *Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer.* J Clin Oncol, 2007. **25**(13): p. 1658-64.
45. Price, T.J., et al., *Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study.* Lancet Oncol, 2014. **15**(6): p. 569-79.

10.0 Appendices

Appendix 1. 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
******NOTE: Please use data reconciliation fax cover sheet to submit***

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 Repor

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

☐ 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

RUTGERS
THE STATE UNIVERSITY OF NEW JERSEY

Appendix 2. 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 sa

SAMPLE FORM
Use customized form provided for the study

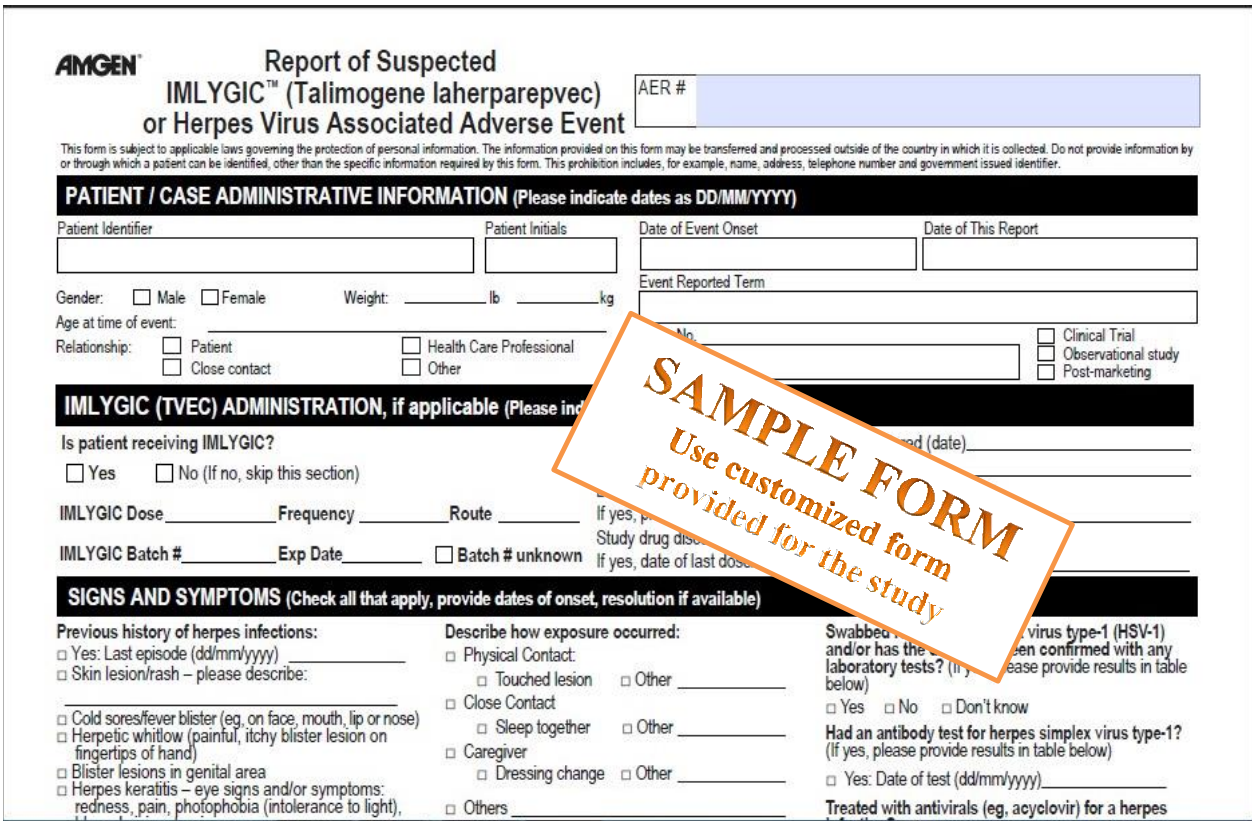
Fax transmission contents (Check all that apply):

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: _____

Appendix 3. 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

No.

☐ Clinical Trial ☐ Observational study ☐ Post-marketing

IMLYGIC (TVEC) ADMINISTRATION, if applicable (Please in

Is patient receiving IMLYGIC?

☐ Yes ☐ No (If no, skip this section)

IMLYGIC Dose_____Frequency _____Route _____

IMLYGIC Batch #_____Exp Date_____ ☐ Batch # unknown

If yes, p

Study drug dis

If yes, date of last dos

ad (date)_____

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 virus type-1 (HSV-1) **and/or has the** een confirmed with any **laboratory tests?** (If y ease provide results in table below)

☐ Yes ☐ No ☐ Don't know

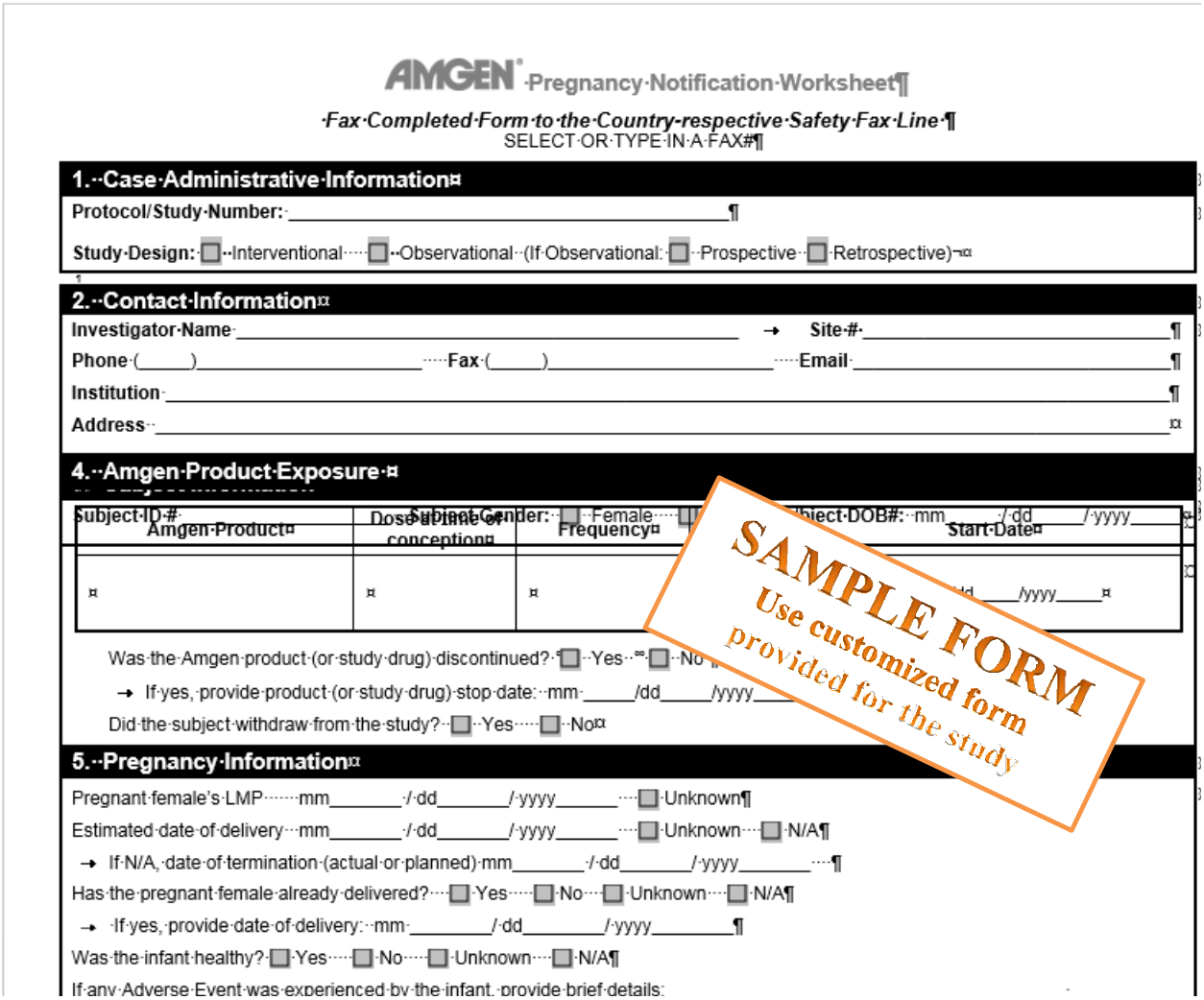
Had an antibody test for herpes simplex virus type-1? (If yes, please provide results in table below)

☐ Yes: Date of test (dd/mm/yyyy)_____

Treated with antivirals (eg, acyclovir) for a herpes

SAMPLE FORM
Use customized form provided for the study

Appendix 4. 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	Start Date
			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 _____

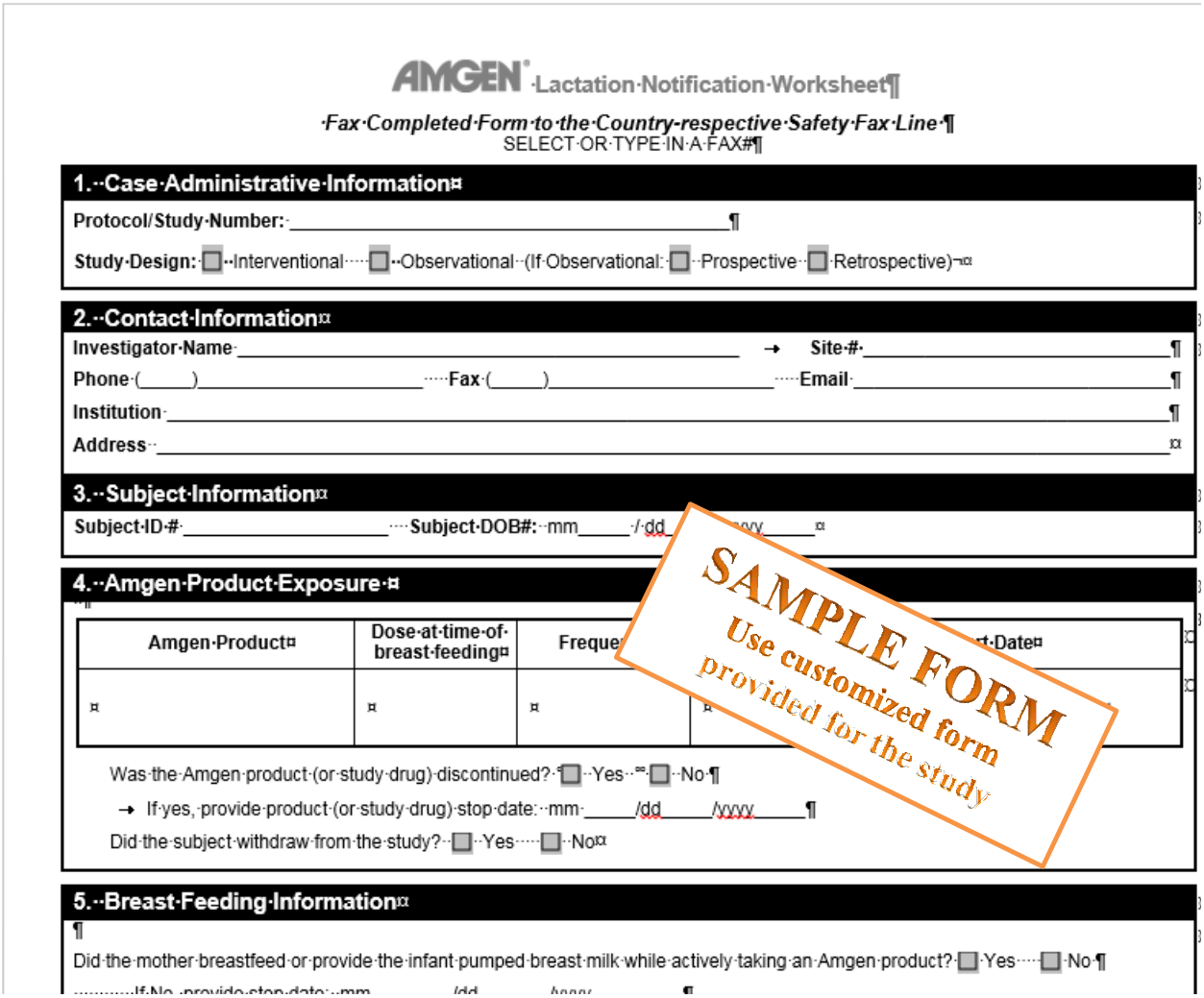
Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

→ 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:

Appendix 5. 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¤	Freque	·t·Date¤
¤	¤	¤	¤

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_____¶