A Phase II Study of Talimogene Laherparepvec (T-VEC) in the Treatment of Locally Advanced Cutaneous Angiosarcoma

NCT03921073

Protocol Version 0.4 Dated 9/18/2019

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Protocol Number: 19878

NCT Identified Number: <NCT#, if available>

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Funded by: Amgen Draft or Version Number: v0.4

Sept 18, 2019

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the Supporting Agency Terms. The Principal Investigator/Sponsor will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Principal Investigator/Sponsor and documented approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed of their obligation to meet the above commitments.

Principal Investigator: John Mullinax, MD
Print/Type Name

Signed: _____ Date: _____

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A phase II study of talimogene laherparepvec (T-VEC) in the treatment of recurrent cutaneous angiosarcoma

Study Description: Seventy-five percent of cutaneous angiosarcoma (CA) patients will eventually fail systemic therapy, and relapsed/refractory patients are left with no known efficacious treatment options. We hypothesize that direct treatment of CA lesions with T-VEC will stimulate local antitumor response, leading to objective responses and prevention of recurrence among enough patients to make this a viable treatment option for the affected population.

Objectives:

Primary Objective: To evaluate the efficacy of T-VEC as treatment for relapsed/refractory cutaneous angiosarcoma

Secondary Objectives:

1. To establish duration of response among treated patients that demonstrate response

2. To measure the duration of progression-free survival among treated patients

3. To measure the complete response rate for lesions that have complete clinical regression following study treatment

4. To monitor adverse events following administration of T-VEC injections

5. To measure the rate of patients requiring surgical resection of T-VEC–treated lesions

Tertiary/Exploratory Objectives:

1. To measure the degree of immune infiltration in surgically resected T-VEC–treated tumors

2. To evaluate surgical outcomes for those patients whose T-VEC–treated tumors are resected

Endpoints:

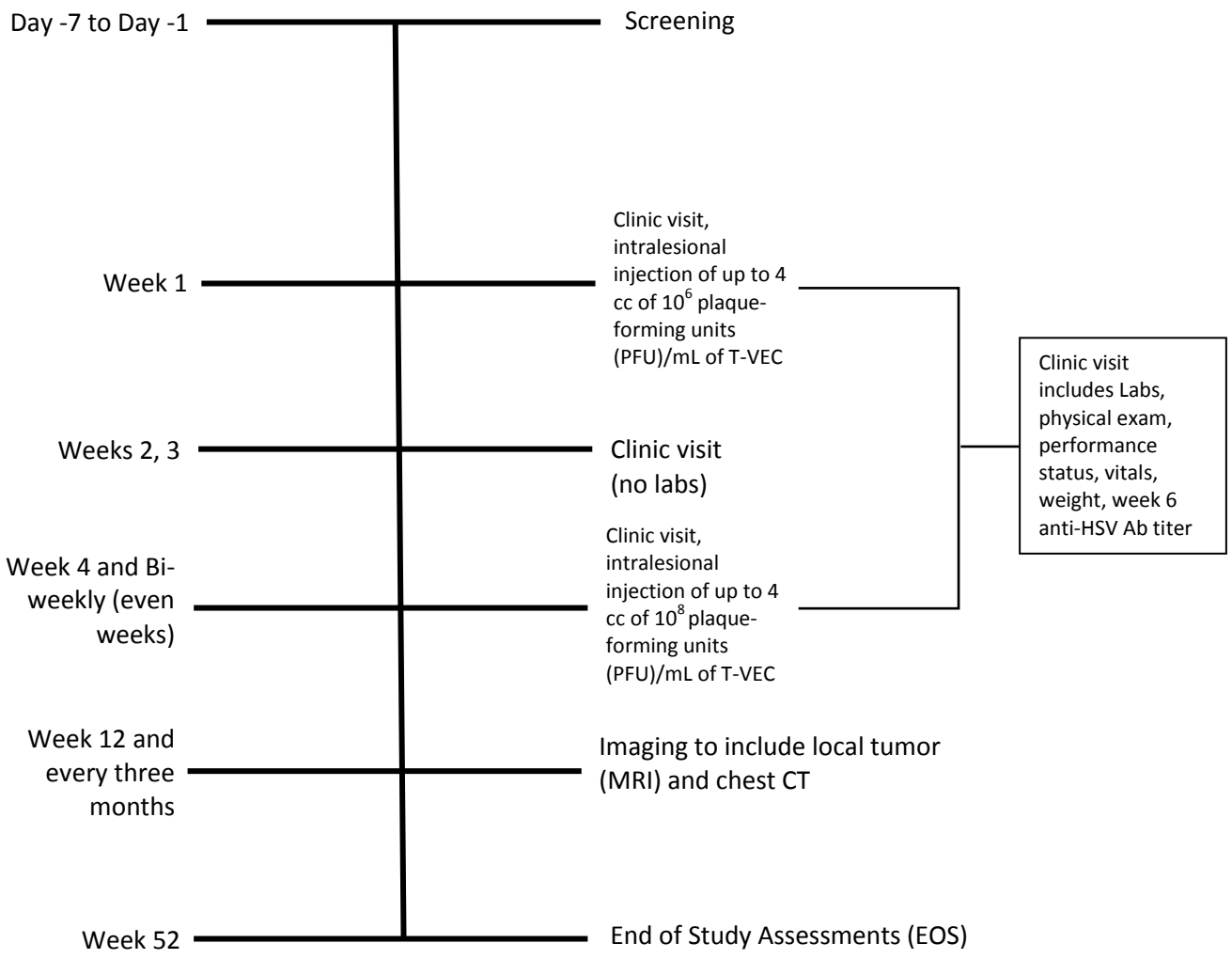
Primary Endpoint: Overall response rate: the proportion of patients to demonstrate complete or partial responses in injected lesions per modified RECIST criteria appropriate for cutaneous neoplasms.

Secondary Endpoints:

1. Response duration will be measured from the time of initial partial response or complete response until documented progression

	2. Progression-free survival: period from time of first injection to progression of disease or appearance of new cutaneous angiosarcoma tumors that were not present at the time of study entry 3. Complete Response rate: proportion of patients with CR, defined as lesions with complete clinical regression 4. Incidence of adverse events from injection of T-VEC into cutaneous angiosarcoma 5. Proportion of patients whose T-VEC–treated tumors require surgical resection **Tertiary/Exploratory Endpoints:** 1. Immunohistochemistry and flow cytometry analyses of immune infiltration within resected tumor specimens 2. Surgical outcomes recorded will include margin status, percent viable tumor, postoperative complications, and disease-free interval following resection.
Study Population:	Thirteen patients with locally advanced recurrent or unresectable cutaneous angiosarcoma
Phase:	Phase II
Description of Sites/Facilities Enrolling Participants:	Moffitt Cancer Center (Tampa, FL), a high-volume, NIH-designated Comprehensive Cancer Center
Description of Study Intervention:	Patients will undergo intralesional injections of up to 4 cc of 10^6 plaque-forming units (PFU)/mL of T-VEC. Dose is dependent on the diameter of the lesions to be injected (volume injected is related to diameter of lesion(s) at time point 0). Three weeks later and every other week thereafter, the patients will be injected with up to 4 cc of 10^8 PFU/mL, with dose dependent on the diameter of the lesion(s) to be injected. Patients may be treated for up to 12 months. A Simon's 2-stage design will be used, assuming that at least a P0 response rate of 10% will be reached for injected lesions. In the first stage, 8 patients will be accrued. If there is > 1 response in these 8 patients, the study will enroll 5 additional patients for a total of 13. The null hypothesis will be rejected if 4 or more responses are observed in 13 patients. This design yields a type I error rate of 0.03 and power of 0.8 when the P1 response rate is 40%.
Study Duration:	The duration of the study, defined as interval from when the study opens to enrollment until completion of data analyses, will be 24 months.
Participant Duration:	12 months

1.2 SCHEMA


Day -7 to Day -1
Screening
Week 1
Clinic visit, intralesional injection of up to 4 cc of 10^6 plaque-forming units (PFU)/mL of T-VEC
Weeks 2, 3
Clinic visit (no labs)
Week 4 and Bi-weekly (even weeks)
Clinic visit, intralesional injection of up to 4 cc of 10^8 plaque-forming units (PFU)/mL of T-VEC
Clinic visit includes Labs, physical exam, performance status, vitals, weight, week 6 anti-HSV Ab titer
Week 12 and every three months
Imaging to include local tumor (MRI) and chest CT
Week 52
End of Study Assessments (EOS)

1.3 SCHEDULE OF ACTIVITIES (SOA)

For explanation of procedures, please see Section 8 (Study Assessments and Procedures).

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Imaging must be done within 4 weeks prior to the start of therapy and then every three months starting at week 12. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Table 1: Schedule of Activities

	Wk -4	Wk -1	Wk 1	Wk 2	Wk 3	Wk 4 and Bi-weekly	Wk 12 and every three months	Off Study[e]
T-VEC[a]			X			X	X	
Informed consent		X						
Demographics		X						
Medical history		X						
Concurrent meds		X	X	X	X	X	X	X
Physical exam		X	X			X	X	X
Imaging	X						X	
Vital signs		X	X	X	X	X	X	X
Height		X						
Weight		X	X	X	X	X	X	X
Performance status		X	X			X	X	X
Complete blood panel w/diff, platelets		X	X			X	X	X
CMP[b]		X	X			X	X	X
EKG		X						
Coagulation studies (PT/PTT/INR)		X						
Adverse event evaluation		X	X	X	X	X	X	X
Tumor measurements – ruler/calipers and digital photography of lesions		X	X	X	X	X	X	X
Punch biopsy[c]		X						X
B-HCG blood pregnancy test		X[d]						

a. Talimogene laherparepvec (T-VEC): Dose as assigned; *administration schedule only applies if tumor is visualized.* Dose 2 to be given 21 days after dose 1 with window of +3 days. Window for remaining doses is +/- 3 days.
b. Comprehensive Metabolic Panel: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, , potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
c. Punch biopsy will be performed using a 4-6 mm punch, up to 2 biopsies per instance.
d. Serum pregnancy test (women of childbearing potential) completed within 72 hours of enrollment.
e. Patients will be treated for a maximum of 52 weeks per section 6.1.2.3. Off-study treatment evaluation should be completed within 30 days after last T-VEC treatment. Patients will continue to be followed-up posttreatment to determine RFS and note any complications; patients will also be followed every 6 months (+/- 1 month) for 2 years by telephone, review of follow-up notes for recurrence status and latent herpetic infection.

2 INTRODUCTION

2.1 STUDY RATIONALE

Talimogene laherparepvec (T-VEC) is an herpes simplex virus type 1- (HSV-1–) based oncolytic virus designed to selectively replicate in tumors and produce granulocyte macrophage colony-stimulating factor (GM-CSF) to stimulate antitumor immune responses. T-VEC is administered by intratumoral injection and is currently under investigation as intralesional therapy for several solid tumor types. Intratumoral injection of T-VEC could result in an influx of infiltrating T cells mediated by direct tumor destruction, potentially initiating an immune response against tumor-associated antigens.

Cutaneous angiosarcoma (CA) is a difficult disease to treat, primarily due to the high recurrence rate and need for wide resection. CA is often associated with a prior history of radiation therapy and can respond well to taxane-based systemic therapy, which has been used effectively in the neoadjuvant setting. Unfortunately, recurrence is experienced by up to 75% of patients, including those treated with combination therapy, and they have no efficacious second-line treatment options available to them. The use of an intralesional immunomodulatory agent like T-VEC represents a novel approach for the treatment of patients whose disease is not controlled by standard therapy and have no other options. An early report of safety using T-VEC in advanced sarcoma patients was presented at ASCO 2018. Three CA patients were enrolled and 2 were classified as responders. The purpose of this trial is to validate this early response signal in a formal phase 2 trial for CA patients.

The goal of injecting T-VEC directly into the tumor is to stimulate both systemic and local anti-tumor responses. The insertion of a GM-CSF gene into the viral genome, as described in Section 2.2.2, will ideally create an adaptive immune response within the tumor, augmenting treatment and furthering the pathway to a complete response of the tumor and hopefully prevention of recurrence of cutaneous angiosarcoma.

2.2 BACKGROUND

2.2.1 DISEASE BACKGROUND

CA is a rare cutaneous neoplasm that is classified as a soft tissue sarcoma which arises within the epidermis or dermis. The disease presents largely as 2 separate phenotypes. In one form, the cause is idiopathic and effects elderly men with a predilection for occurrence in the head and neck region. In another form, the disease is associated with a history of radiation therapy and most commonly affects women, with disease occurring in the skin of the breast after breast conservation therapy for primary breast cancer. The latter form occurs with a median latency period of 7 years between the exposure to radiation and development of a secondary malignancy.

Treatment for either condition is primarily wide surgical resection. Wide margins can be difficult to obtain as anatomic constraints often limit the resection. Even when primary resection is feasible, recurrence is common, with a local recurrence rate up to 60% for those with idiopathic cutaneous angiosarcoma and 75% for those with radiation-associated cutaneous angiosarcoma. Complicating treatment further is the presence of multifocal disease in both the primary and recurrent setting, which is difficult to manage with surgical resection. Despite the known association, radiation therapy has been advocated for cutaneous angiosarcoma as a way to increase local control.

With high local recurrence rates, there is an unmet need for local therapy. The anatomic constraints limiting resection in the primary setting are worse with recurrence and repeat radiation therapy to a site is generally not feasible. Systemic therapy is used for these patients; however, these options are often restricted by the limitations associated with the age of these often elderly patients.

2.2.2 STUDY AGENT

T-VEC (Imlygic), previously known as OncoVexGM-CSF, is a HSV-1–derived oncolytic immunotherapy that selectively replicates within tumors and produces GM-CSF. In talimogene laherparepvec, HSV-1 is modified through deletion of 2 nonessential viral genes, *ICP47* and *ICP34.5*. The deletion of the *ICP47* gene up-regulates the HSV *US11* gene, reduces the suppression of antigen presentation, and enables the virus to grow and replicate within tumor cells. Functional deletion of *ICP34.5* reduces neurotoxicity and enhances tumor-selective replication. The gene encoding GM-CSF is inserted, and its expression promotes dendritic cell activity and increased tumor antigen presentation, potentially inducing greater tumor-specific T cell responses (Figure 1)

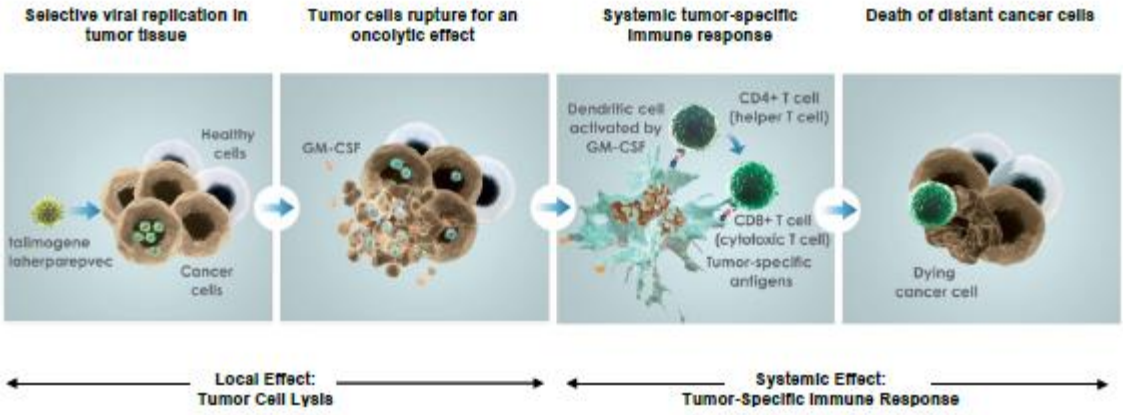


Figure 1. Local and systemic effects of T-VEC.

T-VEC is administered by direct injection into tumors. For the indications currently FDA-approved in melanoma, an optimized dosing regimen consisting of a first dose of 10^6 plaque-forming units (PFU)/mL (total injected volume dependent on injectable tumor diameter) followed by subsequent doses of 10^8 PFU/mL (total injected volume dependent on injectable tumor diameter) is used. This regimen is based on a phase 1 dose-ranging study (001/01) in which this regimen was identified as being well tolerated by both HSV-1 seronegative and seropositive patients. It is anticipated that this regimen will be used in most other oncology indications going forward, including T-VEC in combination with other treatment modalities.

T-VEC is a modified version of HSV-1. HSV-1 has several advantages over other viruses for development as an oncolytic agent. It infects a wide variety of cell types, has a rapid replication cycle resulting in cell lysis, allows the incorporation of single or multiple inserted genes, which may improve the anti-tumor effect, and appropriate titers can be produced in quantities sufficient for clinical use.

Nonclinical and clinical data have shown that selective deletion of HSV genes results in a nonpathogenic virus with promising properties for cancer therapy. The modifications resulting in the enhanced properties of T-VEC include the following:

- Use of a new isolate of HSV-1 (strain JS1), demonstrated to more effectively lyse a variety of human tumor cell lines in vitro than other viruses used in previous clinical studies.
- Functional deletion of the HSV-1 gene encoding ICP47, improving the presentation of tumor antigens following oncolytic virus replication and intended to enhance the anti-tumor immune response.
- Insertion of the gene encoding human GM-CSF, thereby inducing the differentiation and proliferation of dendritic cell precursors in and around the injected tumor and intended to aid the induction of a systemic anti-tumor immune response.

Multiple safety features have also been incorporated into talimogene laherparepvec, including

- Functional deletion of *ICP34.5*, which functions as a virulence factor during HSV infection. This functional deletion limits replication in non-dividing cells and renders the virus non-pathogenic. The safety of ICP34.5 functionally deleted HSV has been shown in multiple clinical studies.
- Insertion of the human GM-CSF coding sequence such that it replaces all of the gene encoding *ICP34.5* to ensure that any potential recombination events between T-VEC and wild-type virus could only result in a disabled, non-pathogenic virus and could not result in the generation of wild-type virus carrying the gene for human GM-CSF.
- The HSV thymidine kinase (TK) gene remains intact, which renders T-VEC sensitive to anti-viral agents such as acyclovir. Therefore, acyclovir could be used to block virus replication, if necessary, although this has never been found to be needed in the patients treated to date.

T-VEC has been tested for efficacy in a variety of in vitro (cell line) and in vivo murine tumor models and has been shown to eradicate tumors or substantially inhibit their growth at doses comparable to those used in clinical studies. Nonclinical evaluation has also confirmed that GM-CSF enhances the immune response generated, enhancing both injected and uninjected tumor responses, and that increased surface levels of MHC class I molecules result from the deletion of *ICP47*.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

2.3.1.1 OVERVIEW OF RISKS

Safety data from the completed OPTiM phase 3 registration study demonstrated the most common side effects of talimogene laherparpvec monotherapy versus GM-CSF were chills (49% versus 9%), pyrexia (43% versus 9%), injection-site pain (28% versus 6%), nausea (36% versus 20%), influenza-like illness (30% versus 15%), and fatigue (50% versus 36%). Adverse events (AE) of grade 3 or greater occurred in 36% of patients receiving T-VEC and 21% of subjects receiving GM-CSF. The only grade 3/4 adverse events occurring in ≥ 5 subjects was cellulitis (6 patients [2.1%] treated with T-VEC; 1 patients [< 1%] treated with GM-CSF). Of 10 fatal adverse events in the T-VEC arm, 8

were attributable to disease progression. The remaining two fatal adverse events (sepsis in the setting of salmonella infection; myocardial infarction) were not considered treatment-related per investigator.

Overall with T-EC, 86% of AEs were grade 1 or 2, although at least one grade 3 or 4 AE was observed in each patient. The investigators considered just two adverse events (pyrexia and fatigue) to be T-VEC-related and occurred in two or more patients. Across all cohorts and severity grades, the most frequent AEs were consistent with chemoradiation delivery. The grade 3 or 4 AEs observed in ≥ 2 patients were unrelated to T-VEC. The AE profile, therefore, may include events related to T-VEC, chemotherapy, radiation, tumor-related signs and symptoms, disease progression, and/or a combination of these. However, the concurrent use of T-VEC, cisplatin, and external beam radiation therapy has not resulted in more frequent or more severe adverse events beyond those typically encountered with these other anti-cancer therapies.

After intratumoral injection, T-VEC is generally cleared from blood and urine of patients within 48 hours. However it can be detected for up to 1 week in the blood of 30% of patients and in the urine of 20% of patients. Low levels of virus have been detected on the surface of injected lesions for up to 2 weeks in 11% of patients. In most cases, this was observed in seronegative patients in the phase 1 study, in which a higher first dose of T-VEC was administered than has been used in subsequent studies. Subsequent studies have therefore used a lower initial dose.

No cases of confirmed infection of non-tumor tissue by T-VEC in treated patients have been reported to date. In the pivotal clinical study, AEs related to HSV infections were reported in 5.5% of patients (n = 16) in the T-VEC group and 1.6% (n = 2) in the GM-CSF group. Most cases (n = 14) were reported as oral herpes, with 1 case each reported as herpes simplex and herpetic keratitis in the T-VEC group. The patient with herpetic keratitis had a history of this event prior to enrollment in the study. Whether the reported lesions were due to wild-type herpes or to T-VEC could not be confirmed as viral testing was not performed.(Andtbacka, Kaufman et al. 2015) T-VEC is now Food and Drug Administration approved in the United States as Imlygic for melanoma, and the prescribing insert can be found at *http://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/imlygic/imlygic_pi.*

2.3.1.2 KNOWN POTENTIAL RISKS FOR T-VEC

Please see T-VEC Investigator's Brochure (IB) for full information and complete listing on important potential risks. Summary of identified risks are included below.

Identified Risk: Injection Site Reactions

Because T-VEC is administered by direct injection into cutaneous, subcutaneous, and nodal tumor masses, injection site AEs may occur, such as erythema, local skin discoloration, induration, warmth, and pain. Infrequently, injected cutaneous tumor masses may undergo necrosis, predisposing patients 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 T-VEC-treated subjects. Most events of injection site pain and injection site reaction in patients receiving T-VEC were mild to moderate in severity. Subjects seronegative at baseline for HSV-1, when given an initial dose of T-VEC 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.

Important Identified Risk: Cellulitis at Site of Injection

Intralesional administration of T-VEC by injection has been associated with cellulitis at the injection site. In some cases, a local inflammatory reaction with localized tumor necrosis developed; in other cases, a bacterial infection developed. In the pivotal clinical study, the incidence of adverse events in the bacterial cellulitis category was 6.2% (n = 18) in the T-VEC group and 1.6% (n = 2) in the GM-CSF group. Seven patients (2.4%) in the T-VEC group and 1 patient (0.8%) in the GM-CSF group experienced serious adverse events (SAEs) of cellulitis. Five of the events (all in the T-VEC arm) were considered to be possibly related to study treatment. Fever, elevated white blood cell count, bacteremia or sepsis, and hospitalization for intravenous antibiotics were reported in 5 of the 7 cases in the T-VEC group.

Important Identified Risk: Accidental Exposure of Health Care Providers to T-VEC

A needle stick injury, spill, or splash-back during administration may result in accidental exposure of health care providers to T-VEC. The *ICP34.5* gene deletion is intended to allow only tumor-selective replication and limited or no viral replication in normal tissues. However, T-VEC injection can result in signs or symptoms of primary infection at the site of exposure. In the event of an accidental exposure to T-VEC, exposed individuals should be advised to clean affected area thoroughly with soap and water and/or a disinfectant. If signs or symptoms of herpetic infection develop, patients should contact their healthcare provider who will call Amgen Medical Information and (1-855-IMLYGIC or 1-855-465-9442). Healthcare providers with direct exposure (needle stick, back splash) or signs/symptoms of herpetic infection will call Amgen Medical Information directly on their own behalf. T-VEC is sensitive to acyclovir. Amgen must be notified and swabs taken of all suspected herpetic outbreaks.

Important Identified Risk: Disseminated Herpetic Infection in Severely Immunocompromised Individuals

Patients with immunosuppression for any reason were excluded from clinical trials with T-VEC. Disseminated herpetic infection in severely immunocompromised individuals is defined as an important identified risk based on the following the nonclinical data and literature. Evidence of lethal systemic viral infection was observed in 100% of severe combined immunodeficiency (SCID) mice (deficient in T and B cells) following intratumoral injection of T-VEC in a mouse colon carcinoma xenograft model. Similar findings were observed in up to 20% of BALB/c nude mice (primarily deficient in T-cell function) following intratumoral injection of T-VEC in Ewing sarcoma and osteosarcoma xenograft models. Viral inclusion bodies and/or necrosis in enteric neurons in the gastrointestinal tract, adrenal gland, and skin were observed in both mouse strains; and in pancreatic islet cells, eye, pineal gland, and brain of SCID mice. Lethality in 100% of animals following intracutaneous injection of wild-type HSV-1 in nude mice has been reported (Hayashida et al, 1982; Yamamoto et al, 1985). The data in T-VEC-treated SCID mice indicated that severe toxicity associated with disseminated viral infection may occur in patients who are severely immunosuppressed. The data in the BALB/c nude mice suggested the potential for toxicity due to T-VEC in patients with less severe immunosuppression. Consistent with the general literature, these data indicate an important role of host defenses, including T and B cells, in the immune response to T-VEC and HSV-1 viruses.

2.3.2 KNOWN POTENTIAL BENEFITS

Please see T-VEC Investigator's Brochure (IB) for full information and complete listing on the clinical efficacy of T-VEC in various tumor types. Summary of efficacy data is included below.

The benefits of T-VEC have been described in five studies when used as monotherapy and another four studies when used in combination therapy for various tumor types. The most extensive experience has been in patients with cutaneous melanoma where overall response rates (ORR) have been reported between 26-28% when used as monotherapy and 50-57% when combined with immune checkpoint inhibitors. The only study report survival

data indicated an increase in overall survival in patients that received T-VEC compared to control subjects that received intralesional GM-CSF (23.3 months vs. 18.9 months, p=0.51).

In reports of T-VEC in other solid tumors, data exists for those with head and neck squamous cell carcinoma. In these patients, the clinical response rate (defined as decrease in size from screening) was 94.6% and the pathologic CR rate for those that underwent resection was 93.3%.

A recent presentation at the American Society of Clinical Oncology meeting in 2018 described the safety and efficacy of T-VEC in combination with pembrolizumab in patients with a variety of soft tissue sarcoma histologic subtypes. In this report, 3 patients with cutaneous angiosarcoma were treated, two of whom demonstrated a partial response. While no patients in the study exhibited complete response, there was an overall response rate of 75% for patients with locally advanced disease. The median time to response was 16 weeks (range 8-32 weeks).

For a full list of potential benefits, please refer to the investigator brochure.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The efficacy of T-VEC in various solid tumor types has been demonstrated in several clinical trials. As an intralesional therapy, this treatment is most promising for patients with locally advanced disease. The primary risks associated with this treatment are injection site reactions and cellulitis surrounding the injection site. These risks are low and expected given the mechanism of action for this therapy. Most of the injection site reactions could be described as a positive indication of an immune-stimulation. Specific risks to this treatment include the potential for infection of healthcare providers or patients due to exposure. Using universal precautions for the injection procedure mitigates this risk to the greatest degree and treatment with acyclovir is available for these rare instances.

The potential benefits for patients with locally advanced cutaneous malignancies outweigh the reported risks. Given the paucity of treatment options for those that have relapsed or recurred with standard treatment, reported response rates of nearly 30% for monotherapy and up to 75% with combination therapy are encouraging. The highest rates of response were seen in the most recent presentation for patients with soft tissue sarcoma where 75% of patients with locally advanced disease experienced and objective response, the vast majority of which were ongoing. The safety profile in this report was quite acceptable with only 1 reported grade 3/4 fever related to T-VEC. There were no reported instances of cellulitis in this study and no mention of injection site reactions.

Taken together, the potential for benefit in these patients outweighs the reported risks from several prior, large clinical trials. The significant experience with this treatment at this institution further supports the safety of administering this treatment. One might argue that the response rates for patients with soft tissue sarcoma may well be due to combination therapy with anti-PD1 therapy, but the results of the SARC-028 clinical trial would suggest otherwise. That trial reported a 10% overall response rate for patients that received anti-PD1 monotherapy for advanced soft tissue sarcoma. While there is no current available data for T-VEC monotherapy in patients with soft tissue sarcoma, the SARC-028 data suggests that the contribution of T-VEC to this response rate is significant. The design of this trial has thus assumed a response rate of 40% for cutaneous angiosarcoma patients given the monotherapy treatment plan.

3 OBJECTIVES AND ENDPOINTS

Table 2: Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
To evaluate the efficacy of T-VEC as treatment for relapsed/refractory cutaneous angiosarcoma	Overall response rate (ORR): the proportion of patients to demonstrate complete or partial responses in injected lesions per modified RECIST criteria appropriate for cutaneous neoplasms at 24 weeks.
Secondary	
1. To establish duration of response among treated patients	1. Response duration will be measured from the time of initial partial response or complete response until documented progression
2. To measure the rate of progression-free survival among treated patients	2. Progression-free survival: period from time of first injection to progression of disease or appearance of new CA tumors that were not present at the time of study entry
3. To measure the complete response (CR) rate for lesions that have complete clinical regression following study treatment	3. Complete Response rate: proportion of patients with pCR, defined as lesions with complete clinical regression
4. To monitor adverse events following administration of T-VEC injections	4. Incidence of adverse events from injection of T-VEC into cutaneous angiosarcoma
5. To measure the rate of patients requiring surgical resection of T-VEC–treated lesions	5. Proporation of patients whose T-VEC–treated tumors require surgical resection
6. To measure the degree of immune infiltration in surgically resected T-VEC–treated tumors	6. Immunohistochemistry and flow cytometry analyses of immune infiltration within resected tumor specimens
Tertiary/Exploratory	
1. To measure the degree of immune infiltration in surgically resected T-VEC–treated tumors	1. Immunohistochemistry and flow cytometry analyses of immune infiltration within resected tumor specimens to determine patterns of lymphocyte infiltration associated with response
2. To evaluate surgical outcomes for those patients whose T-VEC-treated tumors are resected	Surgical outcomes recorded will include margin status, percent viable tumor, postoperative complications, and disease-free interval following resection.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a single-center, single-arm, phase 2 study to evaluate the efficacy of intratumoral injection with talimogene laherparepvec (T-VEC) as monotherapy in relapsed/refractory locally advanced cutaneous angiosarcoma (CA) tumors. The hypothesis is that intralesional therapy using T-VEC will result in an objective response (CR or PR) these patients. There will be no dose modifications from the current FDA-approved dose for other indications. Specific details regarding dosing and administration can be found in section 6.1.2. There are no stratifications in this trial.

Patient enrollment will follow a Simon's 2-stage design, assuming that at least a P0 response rate of 10% will be reached for injected lesions. In the first stage, 8 patients will be accrued. If there is > 1 response in these 8 patients, the study will enroll 5 additional patients for a total of 13. The null hypothesis will be rejected if 4 or more responses are observed in 13 patients. This design yields a type I error rate of 0.03 and power of 0.8 when the P1 response rate is 40%.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

There are several considerations regarding this study design:

1. Dosing
    a. The study drug is currently FDA-approved for cutaneous melanoma with a dosing schedule proven to be safe and effective in several prior clinical trials. We have chosen to use this dose given the proven safety profile and the efficacy shown in a prior phase 2 study of patients with soft tissue sarcoma.
2. Phase 2
    a. The phase 2 design is based on the previously reported data, demonstrating safety with intralesional therapy for locally advanced soft tissue sarcoma patients. A phase 1 design would be duplicitous to this data presented at ASCO 2018 (Kelly, Bowler, et. al)
3. Patient population
    a. Patient with locally advanced cutaneous angiosarcoma have very limited options for treatment. We have limited this trial to locally advanced patients, since the efficacy of control for distant disease (stage IV) has not been demonstrated to nearly the same degree as for patients with locally advanced disease. Gaining control of local disease will yield tremendous benefit for patients with otherwise no treatment options.
4. Response rate
    a. The P1 response rate (40%) is based on prior published response data for similar patients (ORR 75%) when T-VEC was used in combination with checkpoint inhibition. Given that checkpoint inhibitors have very limited efficacy when used alone in patients with sarcoma, the P1 response rate was chosen as it is 10% higher than the reported efficacy for cutaneous melanoma.

4.3 JUSTIFICATION FOR DOSE

Refer to talimogene laherparepvec pharmacy information and Investigator Brochure.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Adult male or female, aged 18 years and over
4. Patients must have histologically confirmed CA without visceral or CNS metastases, with resection deemed of no benefit by technical or oncologic principles, and have progressed on at least one line of systemic therapy
5. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded by digital photography) as ≥6 mm with calipers or a ruler.
6. Easter Cooperative Oncology Group performance status 0-1 (Karnofsky ≥70%).
7. Patients must have normal organ and marrow function as defined below:
    a. Hematological
        i. - Absolute neutrophil count ≥ 1500/mm3 (1.5x109/L)
        ii. - Platelet count ≥75,000/mm3 (7.5x109/L)
        iii. - Hemoglobin ≥8 g/dL (without need for hematopoietic growth factor or transfusion support)
    b. Renal
        i. - Serum creatinine ≤1.5 x upper limit of normal (ULN), OR 24-hour creatinine clearance ≥60 mL/min for subject with creatinine levels > 1.5 x ULN. (Note: Creatinine clearance need not be determined if the baseline serum creatinine is ≤1.5 x ULN. . Creatinine clearance should be determined per institutional standard).
    c. Hepatic
        i. - Serum bilirubin ≤1.5 x ULN OR direct bilirubin ≤ ULN for a subject with total bilirubin level > 1.5 x ULN
        ii. - Aspartate aminotransferase (AST) ≤2.5 x ULN OR <5 x ULN, if liver metastases present and injection does not involve a visceral lesion
        iii. - Alanine aminotransferase (ALT) ≤2.5 x ULN OR <5 x ULN, if liver metastases present and injection does not involve a visceral lesion
    d. Coagulation
        i. - International normalization ratio (INR) or prothrombin time (PT) ≤1.5 x ULN, unless the subject is receiving anticoagulant therapy, in which case PT and partial thromboplastin time (PTT)/ activated PTT (aPTT) must be within therapeutic range of intended use of anticoagulants.
        ii. PTT or aPTT ≤1.5 x ULN, unless the subject is receiving anticoagulant therapy as long as PT and PTT/aPTT is within therapeutic range of intended use of anticoagulants.
8. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to enrollment. If urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients with a second active malignancy, exceptions are localized non-melanoma skin cancers or in situ carcinoma
2. Patients receiving any other investigational agents
3. Participants with tumor(s) in direct contact or encasing a major blood vessel, those with ulceration and/or fungation onto the skin surface, and those with history of re-irradiation or prior lymph node neck dissection to a field involving the carotid arteries
4. History or evidence of active autoimmune disease that requires systemic treatment (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
5. Evidence of clinically significant immunosuppression such as the following:
    a. - Primary immunodeficiency state such as Severe Combined Immunodeficiency Disease.
    b. - concurrent opportunistic infection.
    c. - receiving systemic immunosuppressive therapy (> 2 weeks) including oral steroid doses > 10 mg/day of prednisone or equivalent within 7 days prior to enrollment.
6. Active herpetic skin lesions or prior complications of HSV-1 infection (e.g., herpetic keratitis or encephalitis).
7. Requires intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (e.g., acyclovir), other than intermittent topical use.
8. Previous treatment with talimogene laherparepvec or any other oncolytic virus.
9. Prior therapy with tumor vaccine.
10. Received live vaccine within 28 days prior to enrollment.
11. Prior immunosuppressive, chemotherapy, radiotherapy (in which the field encompassed a planned injection site), biological cancer therapy, or major surgery within 28 days prior to enrollment or has not recovered to CTCAE grade 1 or better from adverse event due to cancer therapy administered more than 28 days prior to enrollment.
12. Prior radiotherapy in which the field does not overlap the injection sites or non-immunosuppressive targeted therapy within 14 days prior to enrollment or has not recovered to CTCAE grade 1 or better from adverse event due to cancer therapy administered more than 14 days prior to enrollment
13. Currently receiving treatment with another investigational device or drug study, or < 28 days since ending treatment with another investigational device or drug study(s).
14. Other investigational procedures while participating in this study are excluded.
15. Known to have acute or chronic active hepatitis B infection, hepatitis C infection, or human immunodeficiency virus (HIV) infection.
16. History of other malignancy within the past 5 years with the following exceptions: adequately treated non melanoma skin cancer, cervical carcinoma in situ, breast ductal carcinoma in situ, or prostatic intraepithelial neoplasia without evidence of disease at the time of enrollment
17. Subject has known sensitivity to talimogene laherparepvec or any of its components to be administered during dosing.
18. Female subject is pregnant or breast-feeding, or planning to become pregnant during study treatment and through 3 months after the last dose of talimogene laherparepvec.
19. Female subject of childbearing potential who is unwilling to use acceptable method(s) of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec.

20. Sexually active subjects and their partners unwilling to use male or female latex condom to avoid potential viral transmission during sexual contact while on treatment and within 30 days after treatment with talimogene laherparepvec.
21. Subjects who are unwilling to minimize exposure with his/her blood or other body fluids to individuals who are at higher risks for HSV-1 induced complications such as immunosuppressed individuals, individuals known to have HIV infection, pregnant women, or infants under the age of 3 months, during talimogene laherparepvec treatment and through 30 days after the last dose of talimogene laherparepvec.

5.3 LIFESTYLE CONSIDERATIONS

- Female subjects cannot be pregnant or breast-feeding, or planning to become pregnant during study treatment and through 3 months after the last dose of talimogene laherparepvec.
- Female subject of childbearing potential must use acceptable method(s) of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec.
- Sexually active subjects and their partners must use male or female latex condom to avoid potential viral transmission during sexual contact while on treatment and within 30 days after treatment with talimogene laherparepvec.
- Subjects must minimize exposure with his/her blood or other body fluids to individuals who are at higher risks for HSV-1 induced complications such as immunosuppressed individuals, individuals known to have HIV infection, pregnant women, or infants under the age of 3 months, during talimogene laherparepvec treatment and through 30 days after the last dose of talimogene laherparepvec.
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.
- Abstain from strenuous exercise for 12 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but do subsequently receive the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a poor performance status may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Both men and women and members of all races and ethnic groups are eligible for this trial. It is anticipated that one patient per month will be accrued. The source of patients will be from the outpatient clinics and general public. The study will be advertised through patient advocacy groups, social media, and flyers in the clinic to increase participation. Given the participation over one year, we will use multiple methods to contact patients including phone, email, and EHR patient portal to ensure continued participation.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

This trial will use talimogene laherparepvec (T-VEC) as monotherapy for the treatment of locally advanced, relapsed/refractory cutaneous angiosarcoma. Full details regarding this drug are included in the Investigator Brochure and pharmacy insert (*http://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/imlygic/imlygic_pi).* Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for T-VEC are described in Section 2.3. Appropriate dose modifications for T-VEC are described in Section 6.1.2.3. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Standard supportive care medications are allowed.

6.1.2 DOSING AND ADMINISTRATION

6.1.2.1 T-VEC TREATMENT PLAN

The first and second injections of T-VEC will be injected into the tumor 3 weeks apart (+3 days) to allow for seroconversion, and then the remaining injections will be given every 2 weeks (+/- 3 days) directly into the primary tumor only, for up to 1 year of injections.

The 10^6 PFU/mL dose will be used for the initial injection (up to 4 mL total volume), while all subsequent injections will be done with 10^8 PFU/mL (up to 4 mL total volume).

6.1.2.2 DOSING AND ADMINISTRATION OF T-VEC

The total volume of T-VEC to be prepared will be based on investigator evaluation of injectable lesions and estimation of the total volume needed based on the T-VEC injection volume guideline based on tumor size table (see below).

The maximum volume of T-VEC 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 T-VEC to be injected into the tumor is dependent on the size of the tumor on ultrasonography on the day of injection and should be determined according to the injection volume guideline in the following table:

T-VEC 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

Administration of T-VEC will follow the specific guidelines and procedure outlined in the Pharmacy Information Guide.

6.1.2.3 DOSING DELAYS/DOSE MODIFICATIONS

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 are not permitted, other than a reduction in the volume injected due to a disease response.

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

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

Subjects who are receiving talimogene laherparepvec may not receive systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir), but may receive a topically administered antiherpetic drug more than 20 cm from a talimogene laherparepvec injection site. Dosing should be permanently discontinued if, in the opinion of the investigator, the subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection). If the subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) for related toxicities, talimogene laherparepvec dosing must be withheld until the corticosteroid dose has decreased to **<** 10 mg prednisone daily (or equivalent).

If talimogene laherparepvec dosing is delayed by more than 4 weeks from the date of the planned dose (ie, 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:

- 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.
- Increase in size ≥2-fold within 4 months of first injection. Patients who develop new locoregional disease during treatment may be treated additionally with the study agent at the PI discretion, in keeping with standard practice for other cancer histologies.
- 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 (ie, 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 (ie, 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.

6.1.3 DURATION OF THERAPY

Patients will be treated for a maximum of 52 weeks with intralesional injection occurring every 2 weeks.

6.1.4 DEFINITION OF DOSE-LIMITING TOXICITY

N/A

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

T-VEC is provided by Amgen Inc.

T-VEC is available as open-label bulk supply that can be used across study participants. T-VEC is supplied in two concentrations, and the concentration that is to be prepared will be based on which visit the administration will occur on:

- T-VEC at nominal concentration of 10^6 PFU/mL with approximately 1.15 mL in a 2 cc vial for the initial dose
- T-VEC at nominal concentration of 10^8 PFU/mL with approximately 1.15 mL in a 2 cc vial for the second and all subsequent doses

Transfer of T-VEC in original packaging or after preparation between clinical sites is not permissible. Contact the study sponsor or Amgen to discuss alternatives for a shipment to arrive at the site where the product is needed.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

T-VEC will be presented as a sterile, semi-translucent to opaque suspension, practically free from particles, preservative-free frozen liquid in a single-use 2.0 cc Crystal Zenith Resin vial. Each vial will contain T-VEC 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 vials are appropriately filled to ensure that a sufficient deliverable dose is provided. Each vial is intended for single use only. Vials will be sealed with gray rubber stoppers, Fluorotec-coated on the product side. The vial caps will be color coded and may be used to help distinguish between the 10^6 PFU/mL and 10^8 PFU/mL vial concentrations.

Information provided on the labels for T-VEC will comply with ICH, GCP, and local regulatory requirements.

6.2.3 PRODUCT STORAGE AND STABILITY

Refer to Pharmacy Information Guide

6.2.4 PREPARATION

Refer to Pharmacy Information Guide

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a single arm, open label study and therefore no blinding or randomization will be used. Bias will be minimized by the photographic documentation of any measurements that document clinical response.

6.4 STUDY INTERVENTION COMPLIANCE

Injection will be performed only by active staff physicians with privileges for "Intralesional Chemotherapy Injections." Any measurements which result in clinical response will be documented by photograph.

6.5 CONCOMITANT THERAPY

N/A

6.5.1.1 EXCLUDED TREATMENTS, MEDICAL DEVICES, AND/OR PROCEDURES DURING STUDY PERIOD

Subjects must not use any of the following therapies during screening or treatment period, unless indicated otherwise:

- Other investigational agents
- Concurrent experimental or approved antitumor therapies other than the study drugs
- Systemic immunosuppressive agents used on an ongoing basis during administration of T-VEC
- Any live vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment and during treatment period. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu - Mist®) are live attenuated vaccines and are not allowed
- Participants may not receive systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir) but may receive a topically administered antiherpetic drug more than 20 cm from a T-VEC injection site

6.5.2 RESCUE MEDICINE

Grade 1 to 2 allergic reactions or febrile states caused by T-VEC cytokine release can be treated with antihistamines and/or acetaminophen as required. In the event any cellulitis is suspected, then appropriate antibiotic therapy should be instituted immediately and further injections stopped until the infection has resolved.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from T-VEC does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding within 4 weeks of last T-VEC injection will be reported as an adverse event (AE).

In the absence of treatment delays due to adverse events, treatment may continue for 12 months or until one of the following criteria apply:

1. Complete response with no cutaneous angiosarcoma to inject
2. Disease progression as per section 8.1.2.3
3. Deterioration in performance status precluding further treatment
4. G4/5 adverse events persisting ≥2 weeks
5. Patient decides to withdraw from the study, or
6. PI decision

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive T-VEC injection for ≥4 weeks (two consecutive doses).

The reason for participant discontinuation or withdrawal from the study will be recorded within the patient's medical record and OnCore and/or the Clinical Trial Management System (CTMS). Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study prior to becoming evaluable for objective response, may be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for two consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant within 24hours and reschedule the missed visit within two weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

8.1.1 PRE-STUDY PROCEDURES

To be performed no more 4 weeks prior to initiation of study treatment

Imaging: CT chest, abdomen, and pelvis with IV contrast

To be performed within 1 week of 1st study treatment evaluation

Informed consent, demographics, concomitant medications, performance status, physical examination, vitals, height, weight, complete blood count, complete metabolic panel, serum pregnancy test completed within 72 hours of enrollment, serum HSV1 Ab, electrocardiogram, tumor measurement by palpation/exam, request slides from tumor biopsies for immunohistochemical analysis.

Week 1 procedures:

Complete blood count, complete metabolic panel, pharmacy to begin thawing/preparation of dose, clinic visit with concurrent medications, performance status, physical examination, vitals, weight, tumor measurement by examination, injection of T-VEC into primary tumor.

Weeks 2, 3 and 6:

Clinic visit with concurrent medications, performance status, physical examination, vitals, weight, anti-HSV Ab titer on week 6 only

Bi-weekly procedures starting Week 4-week 52:

Complete blood count, complete metabolic panel, pharmacy to begin thawing/preparation of dose, clinic visit with concurrent medications, performance status, physical examination, vitals, weight, tumor measurement by examination, injection of T-VEC into primary tumor.

Off-study procedures:

Complete blood count, complete metabolic panel, clinic visit with concurrent medications, performance status, physical examination, vitals, weight, and punch biopsy all within 30 days of last study treatment. Follow up of any treatment-related adverse events until resolution, stabilization, or death for a minimum of 30 days after last study treatment. Data on any perioperative complications should be also collected as applicable. Final tumor

measurement/assessment will be done based on the postoperative pathology report when available in the electronic medical record to assess degree of pathologic response to neoadjuvant therapy. Long-term follow up for disease recurrence/vital status/occurrence of any suspected herpetic infectious events up to 2 years after the off study visit date by telephone contact and/or clinical assessment at least once every 6 months (+/- 1 month) should be done. Patients and their close contacts should be instructed to notify the study team immediately regarding any suspected new herpetic infection events so that clinical evaluation of the event by the patient's health care provider, PCR testing of any lesions, expedited reporting (within 24 hours of notification) to Amgen at 1-855-465-9442 and to the FDA, and treatment as clinically indicated can be completed.

8.1.2 EFFICACY ANALYSES

For the purposes of meeting the secondary endpoints of this study, patients will be re-evaluated for response every 2 weeks prior to injection using physical examination and measurement with calipers and/or ruler.

In addition to baseline imaging, imaging should also be obtained *12* weeks following initial documentation of objective response.

8.1.2.1 DEFINITIONS

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with T-VEC

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least three injections at the 10^8 dose level, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 6 mm by calipers on clinical examination. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 6 mm are considered non-measurable disease.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

"Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), but in addition should be those that lend themselves to

reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. All target lesions will also be injected lesions.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up. All non-target lesions will not be injected with T-VEC.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 6 mm diameter as assessed using calipers. Documentation by color photography at baseline, including a ruler to estimate the size of the lesion, is recommended.

8.1.2.2 GUIDELINES FOR EVALUATION OF CLINICAL DISEASE

All measurements of a palpable lesion should be taken and recorded in metric notation using a ruler or calipers at each study visit. If the lesion is not present, then it should be noted as such in the patient EMR.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

8.1.2.3 RESPONSE CRITERIA

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator). Photography of these changes is recommended.

Evaluation of Best Overall Response

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

Overall Response Criteria

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required**
CR	CR	No	CR	≥ 4 wk Confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 wk Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 wk from baseline
PD	Any	Yes or No	PD	No prior SD, PR, or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.				

Objective response—Response and progression will be evaluated in this study using a primary endpoint of objective response, which is defined as either complete or partial response

8.1.2.4 DURATION OF RESPONSE

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

8.1.2.5 PROGRESSION-FREE SURVIVAL

Progression-free survival is defined as the duration of time from start of treatment to time of progression or death, whichever comes first.

8.1.2.6 FOLLOW-UP PERIOD

The study will continue to follow patient's recurrence/vital status and any evidence of latent herpetic infection up to 2 years out from the start of injections, by reviewing routine clinic visit notes and/or telephone contact every six months (see also section 7).

8.1.2.7 PATHOLOGIC RESPONSE REVIEW

Pathology from biopsies will be reviewed for response by Moffitt Cancer Center (MCC) pathologists.

8.2 SAFETY AND OTHER ASSESSMENTS

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a).

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

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

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

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient.

All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate case report form (CRF). Information to be collected will include event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

All events beginning with start of study intervention until 30 days after the last day of study intervention will be reported. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.]

Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. All adverse events will be documented in electronic medical records, and staff will maintain an adverse event log for each patient. The principal or treating physician will determine toxicity grade and attribution to the study drug, talimogene laherparepvec, with final approval within 10 working days of the assessment. The completed and signed-off logs will be provided for data entry to the assigned data manager within 24 hours of the sign off. The adverse event data entry will be completed within 10 working days. All adverse events must be followed to resolution or stabilization for a minimum of 30 days after last protocol treatment, or death (whichever occurs first) and updated at the time of the next assessment, treatment, discontinuation, or completion. All logs must be available for review and audit. All deaths that occur while the subject is receiving the study drug and/or a minimum of 30 days after administration will be reported as a serious adverse event.

Serious adverse events will be reported to the Protocol Monitoring Committee, the FDA, the Manager of the Institutional Regulatory Affairs, and Amgen within 24 hours (1 day) of learning of the event. All SAEs will be reported to the Clinical Trial Office of Moffitt Cancer Center in 24 hours via the CTO SAE Right Fax (813-449-8486). Serious adverse events will be reported to the Institutional Review Board (IRB) according to IRB policy. This includes new herpetic infections in talimogene laherparepvec-treated patients or their close contacts as required by Amgen and the FDA. The initial report submitted via MedWatch form to the Office of Institutional Regulatory Affairs for Investigation Drugs and Devices must be as complete as possible, including details of the current illness and serious adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the serious adverse event is required if it is not documented in the initial report.

The Moffitt Office of Institutional Regulatory Affairs will complete the necessary documents and provide the report to the FDA as an official submission to the IND. This will occur independently of any other use of the MedWatch form or required reporting of serious adverse events. Submission of the MedWatch form to any other agency,

including the FDA, does not fulfill this IND Safety Reporting requirement. Follow-up to the safety report must also be submitted to the Office of Institutional Regulatory Affairs in a timely manner.

Upon completion of the report, a copy of all initial and follow-up MedWatch forms will be faxed to Manager, Moffitt Office of Institutional Regulatory Affairs, with call or email made to confirm receipt.

For unexpected fatal or life-threatening experiences associated with the use of the investigational product(s), the Office of Institutional Regulatory Affairs will be contacted within 24 hours. Additionally, the Clinical Trial Office of Moffitt Cancer Center will be alerted within 24 hours of the event via the CTO SAE Right Fax (813-449-8486). Notification to Amgen will be made within 24 hours (1 day) of the event. Notification to the FDA will be made as soon as possible, but no later than 7 calendar days after initial receipt of the information.

Safety information for Amgen, the supplier of talimogene laherparepvec, will be exchanged as follows: All serious adverse events will be sent in individual report forms batched every 90 days. Suspected unexpected SAEs will be submitted at the time of regulatory submission, which will be within seven working days. Adverse drug reactions that are not serious will be sent as a listing at the end of the study. Product complaints, medication errors or overdoses, misuse, abuse, transmission of infectious agent, or unauthorized use (when associated with an adverse event) will be sent to Amgen within one working day of sponsor awareness. Amgen should be notified of patients who become pregnant during the trial within 10 days of the sponsor awareness. Amgen does not require notification of events that are not considered related to talimogene laherparepvec, regardless of seriousness and events of interest.

Safety data for Amgen should be sent in the following fashion:
Global Safety Triage Room
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Preferred - Fax: 888-814-8653

8.3 Biomarker, Correlative, and Special Studies or Other Endpoints

8.3.1 ANALYSIS OF TUMOR-INFILTRATING LYMPHOCYTES FROM TUMOR SPECIMENS

Background: We have recently completed a pilot protocol that focused on the immune infiltrate of 15 patient-derived sarcoma specimens. In this sample, 57% were high-grade tumors, 36% were recurrent tumors, and 29% had preoperative therapy. Analysis of tumor digest showed that 48% (range, 3.6%-76%) of cells from the lymphocyte gate were CD3+. There is significant heterogeneity of the immune infiltrate phenotype with respect to CD3+CD8+ fraction within the tumor digest between samples and much more so than seen in the prior experience from melanoma in our laboratory. Tumor-infiltrating lymphocytes (TIL) were grown from fragments of all specimens with TIL observed in 152 of 192 (79%) fragments. The phenotype of the CD3+ subpopulations from TIL cultures included an average 50% (range, 13%-91%) CD8+ and 34% (range, 5%-79%) CD4+ cells.

Methods: The tumor sample obtained from punch biopsy will be minced, placed in a conical vial with rotating agitator (C tube), and processed on a gentleMACS tissue dissociator (Miltenyi Biotec). The C tube will be incubated at 37°C between gentleMACS mechanical disruption cycles. Resulting digest will be filtered through 100-µm filters and counted to verify the tumor cell component, TIL component, and viability. Digest suspension (5×10^5 cells) will be placed in a 48-well plate in culture media containing 6000 IU/mL of IL-2 to generate TIL cultures from the primary tumor. To determine the phenotype of the TIL, flow cytometry will be conducted on the TIL culture. The

tumor immune filtrate will be characterized using a standard, validated panel of antibodies to determine the expression of CD3, CD4, CD8, CD16, and CD56. To determine the activation status of the TIL, flow cytometry using intracellular interferon-gamma staining techniques will be performed.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a).

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

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

8.4.3 CLASSIFICATION OF AN ADVERSE EVENT

8.4.3.1 SEVERITY OF EVENT

All AEs will be graded using the CTCAE 5.0 criteria.

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.

Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.4.3.2 RELATIONSHIP TO STUDY INTERVENTION

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (eg, the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (eg, the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (eg, the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.3.3 EXPECTEDNESS

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.4.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient.

All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate case report form (CRF). Information to be collected will include event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

All events beginning with start of study intervention until 30 days after the last day of study intervention will be reported. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4.5 ADVERSE AND SERIOUS ADVERSE EVENT REPORTING

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient.

All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate case report form (CRF). Information to be collected will include event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

All events beginning with start of study intervention until 30 days after the last day of study intervention will be reported. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.]

Data will be captured in Oncore, MCC's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to MCC Monitoring Policies. All adverse events will be documented in electronic medical records, and staff will maintain an adverse event log for each patient. The principal or treating physician will determine toxicity grade and attribution to the study drug, T-VEC, with final approval within 10 working days of the assessment. The completed and signed-off logs will be provided for data entry to the assigned data manager within 24 hours of the sign off. The adverse event data entry will be completed within 10 working days. All adverse events must be followed to resolution or stabilization for a minimum of 30 days after last protocol treatment, or death (whichever occurs first) and updated at the time of the next assessment, treatment, discontinuation, or

completion. All logs must be available for review and audit. All deaths that occur while the subject is receiving the study drug and/or a minimum of 30 days after administration will be reported as a serious adverse event.

Serious adverse events will be reported to the Protocol Monitoring Committee, the FDA, the Manager of the Institutional Regulatory Affairs, and Amgen within 24 hours (1 day) of learning of the event. All SAEs will be reported to the Clinical Trial Office of MCC in 24 hours via the CTO SAE Right Fax (813-449-8486). Serious adverse events will be reported to the Institutional Review Board (IRB) according to IRB policy. This includes new herpetic infections in T-VEC-treated patients or their close contacts (see Section 7.2) as required by Amgen and the FDA. The initial report submitted via MedWatch form to the Office of Institutional Regulatory Affairs for Investigation Drugs and Devices must be as complete as possible, including details of the current illness and serious adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the serious adverse event is required if it is not documented in the initial report.

Upon completion of the report, a copy of all initial and follow-up MedWatch forms will be faxed to Manager, MCC Office of Institutional Regulatory Affairs, with call or email made to confirm receipt.

For unexpected fatal or life-threatening experiences associated with the use of the investigational product(s), the Office of Institutional Regulatory Affairs will be contacted within 24 hours. Additionally, the Clinical Trial Office of MCC will be alerted within 24 hours of the event via the CTO SAE Right Fax (813-449-8486). Notification to Amgen will be made within 24 hours (1 day) of the event. Notification to the FDA will be made as soon as possible, but no later than 7 calendar days after initial receipt of the information.

8.4.6 SAFETY DATA EXCHANGE FOR 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 the tables below.

Table 1. Expedited Reporting Requirements for Interventional Studies

Safety Data	Timeframe for Submission to Amgen
Suspected Unexpected Serious Adverse Reaction (SUSARs)	Individual reports sent to Amgen at time of expedited reporting to IRB and/or FDA.
Serious Adverse Events (SAEs) (related)	Individual reports sent to Amgen at time of expedited reporting to IRB and/or FDA
Pregnancy/Lactation	Individual reports sent within 10 days of Sponsor/Investigator awareness. (Refer to Appendix 6.4 and Appendix 6.5 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 2. Aggregate Reports

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

In addition to the requirements outlined in Table 1 and 2, 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. HCPs involved in your clinical trial who were directly exposed to talimogene laherparepvec (e.g., needle stick, splash back) but who are without signs or symptoms of herpetic illness should be reported to Amgen at 1-855-IMLYGIC (1-855-465-9442).

Suspected herpetic events 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 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.

Reporting Process for ISS Treated Patients:

- Any suspected herpetic lesion should be reported to Amgen at 1-855-IMLYGIC (1-855-465-9442), evaluated by the Sponsor/Investigator and swabbed for qPCR testing.
- Once an initial report has been made, additional materials will be provided, including reporting forms and supplies needed for shipment of swab samples. Amgen will require patient consent for qPCR testing, which must be obtained prior to swabbing.

Reporting Process for HCPs and Close Contacts:

- Sponsor/Investigator should advise any HCPs and/or Close Contacts with suspected herpetic lesions to contact their personal physician to facilitate reporting to Amgen. Suspected herpetic lesions can be reported by the Sponsor / Investigator, personal physician or exposed individual to Amgen at 1-855-IMLYGIC (1-855-465-9442). Once an initial report has been made, additional materials will be provided,

including reporting forms and supplies needed for the shipment of swab samples. Amgen will require patient consent for qPCR testing, which must be obtained prior to swabbing

Table 3. Accidental Exposure & Herpetic Event Reporting Requirement Summary

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

Additionally, Amgen requires annual submission of IND annual report safety data, as well as an End of Study Report at the time of ISS sponsor submission to the Institutional Review Board (IRB; no later than one calendar year from study completion).

Serious adverse events will be reported to the Protocol Monitoring Committee, the FDA, the Manager of the Institutional Regulatory Affairs, and Amgen within 24 hours (1 day) of learning of the event. All SAEs will be reported to the Clinical Trial Office of Moffitt Cancer Center in 24 hours via the CTO SAE Right Fax (813-449-8486). Serious adverse events will be reported to the Institutional Review Board (IRB) according to IRB policy. This includes new herpetic infections in talimogene laherparepvec-treated patients or their close contacts as required by Amgen and the FDA. The initial report submitted via MedWatch form to the Office of Institutional Regulatory Affairs for Investigation Drugs and Devices must be as complete as possible, including details of the current illness and serious adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the serious adverse event is required if it is not documented in the initial report.

The Moffitt Office of Institutional Regulatory Affairs will complete the necessary documents and provide the report to the FDA as an official submission to the IND. This will occur independently of any other use of the MedWatch form or required reporting of serious adverse events. Submission of the MedWatch form to any other agency, including the FDA, does not fulfill this IND Safety Reporting requirement. Follow-up to the safety report must also be submitted to the Office of Institutional Regulatory Affairs in a timely manner.

Upon completion of the report, a copy of all initial and follow-up MedWatch forms will be faxed to Manager, Moffitt Office of Institutional Regulatory Affairs, with call or email made to confirm receipt.

For unexpected fatal or life-threatening experiences associated with the use of the investigational product(s), the Office of Institutional Regulatory Affairs will be contacted within 24 hours. Additionally, the Clinical Trial Office of Moffitt Cancer Center will be alerted within 24 hours of the event via the CTO SAE Right Fax (813-449-8486). Notification to Amgen will be made within 24 hours (1 day) of the event. Notification to the FDA will be made as soon as possible, but no later than 7 calendar days after initial receipt of the information.

Safety information for Amgen, the supplier of talimogene laherparepvec, will be exchanged as follows: All serious adverse events will be sent in individual report forms batched every 90 days. Suspected unexpected SAEs will be submitted at the time of regulatory submission, which will be within seven working days. Adverse drug reactions that are not serious will be sent as a listing at the end of the study. Product complaints, medication errors or overdoses, misuse, abuse, transmission of infectious agent, or unauthorized use (when associated with an adverse event) will be sent to Amgen within one working day of sponsor awareness. Amgen should be notified of patients who become pregnant during the trial within 10 days of the sponsor awareness. Amgen does not require notification of events that are not considered related to talimogene laherparepvec, regardless of seriousness and events of interest.

Safety data for Amgen should be sent in the following fashion:
Global Safety Triage Room
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Preferred - Fax: 888-814-8653

8.4.7 REPORTING EVENTS TO PARTICIPANTS

n/a

8.4.8 EVENTS OF SPECIAL INTEREST

n/a

8.4.9 REPORTING OF PREGNANCY

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Protocol Monitoring Committee (PMC) of the institution. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the PMC/study sponsor within 24hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the PMC/study sponsor within 24 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 24 hours of the IRB's receipt of the report of the problem from the investigator.

8.5.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

n/a

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

For the primary endpoint, the optimal two-stage design to test the null hypothesis that P0 ≤ 0.10 versus the alternative that P1 ≥ 0.40.

9.2 SAMPLE SIZE DETERMINATION

For the primary endpoint, the optimal two-stage design to test the null hypothesis that P0 ≤ 0.10 versus the alternative that P1 ≥ 0.40 has an expected sample size of 8.93 and a probability of early termination of 0.813. If the treatment is actually not effective, there is a 0.031 probability of concluding that it is (the target for this value was 0.050). If the treatment is actually effective, there is a 0.198 probability of concluding that it is not (the target for this value was 0.200). After testing the treatment on 8 patients in the first stage, the trial will be terminated if 1 or fewer responds. If the trial goes on to the second stage, a total of 13 patients will be studied. If the total number responding is less than or equal to 3, the treatment is rejected.

9.3 POPULATIONS FOR ANALYSES

The analysis datasets (e.g., which participants will be included in each analysis) include the following:

- Intention-to-Treat (ITT) Analysis Dataset
- Safety Analysis Dataset: defines the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of study intervention)
- Per-Protocol Analysis Dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (e.g., participants who took at least 80% of study intervention for 80% of the days within the maintenance period)

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

For the primary endpoint, we will use the Simon's two stage approach as described in detail above in the Sample Size Determination Section. For the secondary endpoints we will use descriptive statistics as well as the Kaplan-Meier approach for the time to event endpoints.

All analyses will be performed in either SAS v. 9.4 or R software using standard procedures and packages.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Our primary endpoint for this analysis will be confirmed overall response rate (ORR) in injected lesions based on modified RECIST criteria appropriate for cutaneous neoplasms (ORR = complete response + partial response)

According to the Simon's two-stage design, after testing the treatment on 8 patients in the first stage, the trial will be terminated if 1 or fewer responds. If the trial goes on to the second stage, a total of 13 patients will be studied. If the total number responding is less than or equal to 3, the treatment is rejected. Please see Sample Size description above for further details.

In addition, we will construct a 95% exact confidence interval for the ORR.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For all secondary endpoints except those with time-to-event responses, we will use basic descriptive statistics such as the mean, median, standard deviation and range for continuous variables and frequencies for categorical variables. We will construct exact 95% confidence intervals to describe these secondary endpoints.

For time-to-event responses, we will use Kaplan-Meier estimates and plots to describe the endpoints. Response duration is measured from the time of first injection to initial partial response or complete response. Progression free survival is measured from time of first injection to progression of disease or appearance of new CA, not present at the time of study entry. The median progression-free survival will be reported with 95% confidence interval.

All secondary endpoints are for descriptive purposes, and no power analyses have been performed for them.

9.4.4 SAFETY ANALYSES

Safety will be analyzed using descriptive reporting of all AE. Toxicity will be reported by type, frequency and severity in tabular format. Final reporting will include reasons for discontinuation related to the study drug. Monthly PMC meeting review of AE/SAE will serve as guidance to PI regarding the rate of AEs for each organ system based on CTCAE v4.03.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Given the study design and patient enrollment, descriptive statistics will not be used to stratify or perform subgroup analyses. Baseline descriptive characteristics will be described using standard descriptive statistics including the mean, median, standard deviation and range for continuous variables and frequencies for categorical variables. We will not use inferential statistics here as the purpose is descriptive only in nature.

9.4.6 PLANNED INTERIM ANALYSES

Please see the Sample Size section about describing in detail the Simon's two-stage approach that we will be using. According to the Simon's two-stage design, after testing the treatment on 8 patients in the first stage, the trial will be terminated if 1 or fewer responds.

We do not plan any other interim analyses.

9.4.7 SUB-GROUP ANALYSES

There will be no subgroup analysis given the overall sample size of this trial.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

There are no planned listings of data by measure and time point.

9.4.9 EXPLORATORY ANALYSES

Exploratory endpoints will be reported by descriptive statistical methods.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The informed consent document is submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at Moffitt Cancer Center. After the study is completed, the de-identified, archived data will be transmitted to and stored at Moffitt Cancer Center, for use by other researchers including those outside of the study. Permission to transmit data to collaborators with established Material Transfer Agreements will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the laboratory of the PI. These samples could be used to research the causes of cancer, its complications and other conditions for which individuals with cancer are at increased risk, and to improve treatment. The PI will retain a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the Mullinax Lab.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
John Mullinax, MD
Moffitt Cancer Center
12902 Magnolia Drive
(813) 745-8736
John.Mullinax@Moffitt.org

The study will be staffed by a Clinical Trial Coordinator who will work with PI to ensure that reporting requirements are met. The Protocol Monitoring Committee at Moffitt Cancer Center will review all study amendments, deviations, AEs, and SAEs.

10.1.5 SAFETY OVERSIGHT

Serious Adverse Events: Serious Adverse Events (SAEs) from this protocol will be reported concurrently to the IRB and the study sponsor. The Protocol Monitoring Committee (PMC) will review these SAEs in accordance with the protocol-specific DSMP. The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results. This trial will be continuously monitored by the PI and the research team and reviewed at weekly Sarcoma Research Group meetings. Safety and monitoring reports will be submitted to the PMC after each patient completes 12 weeks of treatment more frequently if requested by the PMC. A final safety and monitoring report will be submitted to the PMC within three months of defining the MTD. This protocol will be subject to periodic internal audits based on risk or as recommended by the PMC.

10.1.6 CLINICAL MONITORING

MCC's Internal Monitors will periodically monitor regulatory documents and case report forms according to the protocol specific clinical monitoring plan. Monitoring will include review of data for accuracy, completeness, and source verification, reporting of SAEs, and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data will be captured in OnCore and/or MCC's electronic Clinical Trials Management System. For each subject enrolled, the electronic CRF must be completed by the assigned data manager or other authorized study staff. Any paper forms should be typed or filled out indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his/her authorized delegate. This also applies to records for those subjects who fail to complete the study. If a subject stops dosing or terminates from the study, the dates and reasons must be noted on the CRF.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Oncore, a 21 CFR Part 11-compliant data capture system provided by MCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to Amgen. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP. Deviations must be entered into the Clinical Trials Management System (CTMS).

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of the primary endpoint by contacting <specify person or awardee institution, or name of data repository>.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.]

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

AE	Adverse Event
CA	Cutaneous angiosarcoma
CFR	Code of Federal Regulations
CRF	Case Report Form
CTMS	Clinical Trial Management System
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GM-CSF	Granulocyte macrophage colony-stimulating factor
GWAS	Genome-Wide Association Studies
HSV	Herpes simplex virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Investigational Review Board
ISO	International Organization for Standardization
MCC	Moffitt Cancer Center
NIH	National Institutes of Health
ORR	Overall response rate
PFU	Plaque-forming unit
PI	Principal Investigator
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
TIL	Tumor-infiltrating lymphocytes
T-VEC	Talimogene laherparepvec

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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12 APPENDICES

12.1 APPENDIX A

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.