A Phase 1/2 Study of Talimogene laherparepvec in Combination with Neoadjuvant Chemotherapy in Triple Negative Breast Cancer

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TITLE: A Phase 1/2 Study of Talimogene laherparepvec in Combination with Neoadjuvant Chemotherapy in Triple Negative Breast Cancer

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SCHEMA/SYNOPSIS

TRIAL DESIGN: Phase 1 with 3+3 design, and Simon two stage phase 2. The phase 1 is a 3+3 design with two dose levels (DL1: 10^6 PFU for all five injections, DL2: 10^6 PFU 1st injection followed by 10^8 PFU for remaining injections)
STUDY POPULATION: Triple negative breast cancer, non-metastatic undergoing neoadjuvant chemotherapy with dose dense AC-T
RATIONALE: Talimogene laherparepvec is an oncolytic virus that can result in direct tumor destruction along with stimulation of an immune response against tumor antigens that can lead to an influx of infiltrating T cells. Paclitaxel can lead to a similar effect in breast tumors treated with neoadjuvant therapy. These inflamed tumors appear to respond better to neoadjuvant therapy. The goal is to combine these therapies to enhance pathologic complete response rates.
PRIMARY ENDPOINTS: Phase 1: Safety/toxicity, MTD/RP2D Phase 2: Pathologic complete response rate
SECONDARY ENDPOINTS: Immunologic correlates by IHC and T cell receptor sequencing, 5 year RFS/OS, additional biomarkers
STUDY TREATMENT: Patients will undergo weekly paclitaxel 80mg/m2 x 12 weeks initially and get up to 5 talimogene laherparepvec injections on weeks 1, 4, 6, 8, 10. This will be followed by 4 doses of dose dense doxorubicin/cyclophosphamide 60/600 mg/m2 intravenously every 2 weeks. Patients will undergo two ultrasounds on an injection day, one to measure the tumor for dosing of the virus, and the second to guide the injection into the primary tumor where the virus will be injected. If no tumor can be visualized on ultrasound then no more virus injections will be given and the patient will proceed on with the rest of their chemotherapy as planned. An on treatment biopsy will be collected prior to week 6 treatment. Patients will then undergo surgery and will be assessed for the primary endpoint, pathological complete response. Patients will be followed for up to 5 years after completion of study therapy at least once every 6 months for recurrence, death, and any new herpetic infections by telephone and/or clinical evaluation during routine follow up visits.
STATISTICS/SAMPLE SIZE: The phase I 3+3 design with two dose levels would enroll between 9-12 patients. The phase II Simon two stage optimal design would enroll 12 evaluable patients in the first stage, and 25 evaluable patients in the second stage (total n=37). Four or more pathologic complete responses are required in the first stage and 15 or more pathologic complete responses are required to declare the trial positive upon completion of the second stage. This is based on the null hypothesis complete response rate of 30%, alternative hypothesis with 45% complete response rate with a power of .70 and one sided type 1 error of .099.

Baseline	• Consent/Screening • Clipping of primary
Week 1	• US measurement • Paclitaxel + TL injection
Week 2	• Paclitaxel
Week 3	• Paclitaxel
Week 4	• US measurement • Paclitaxel + TL injection
Week 5	• Paclitaxel
Week 6	• US measurement • Paclitaxel + TL injection
Week 7	• Paclitaxel
Week 8	• US measurement • Paclitaxel + TL injection
Week 9	• Paclitaxel
Week 10	• US measurement • Paclitaxel + TL injection
Week 11	• Paclitaxel
Week 12	• Paclitaxel
Week 13-21	• AC q2weeks x 4
Week ~24-25	• Surgery
Years 1-5	• Telephone/chart FU q6 months

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AE	Adverse Event
ANCOV	Analysis of Covariance
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
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
LSMEA	Least Squares Means
MedDR	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NIH	National Institutes of Health
NIH IC	NIH Institute & Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem

US	United States

OBJECTIVES

1.1. Primary endpoint(s): Phase 1: Determine the MTD/RP2D of talimogene laherparepvec administered with neoadjuvant paclitaxel-doxorubicin/cyclophosphamide chemotherapy, safety/toxicity of the combination. Phase 2: Determine the efficacy (evaluated as pathologic complete response rates) of neoadjuvant talimogene laherparepvec in conjunction with neoadjuvant chemotherapy for early/locally advanced triple negative invasive breast cancer

1.2. Secondary endpoints: 5 year recurrence free survival/overall survival, immune activation correlatives by IHC and T cell receptor sequencing

2. BACKGROUND

2.1. Study Disease

Triple negative breast cancer (TNBC) comprises approximately 15-18 percent of breast cancer diagnoses. TNBC is associated with a poorer prognosis overall and is an area of unmet need in breast cancer. It is typically more common among African-American women and/ or young women. Almost a fifth of women diagnosed with TNBC are less than 40 years of age. Overall, these tumors are typically high grade with a high proliferative rate, making them an ideal target for oncolytic immunotherapy.

Current systemic treatment is a combination chemotherapy regimen using either docetaxel/cyclophosphamide for very early stage 1 disease or doxorubicin/cyclophosphamide/taxane combination therapy for higher risk disease. Data from trials such as ECOG 1199, CALGB 9741, and recently SWOG 0221 suggest that the dose dense schedule of doxorubicin/cyclophosphamide followed by either dose dense or weekly paclitaxel is currently the optimal schedule for high risk disease.(1-3) This is the basis for the treatment schedule used in this study. Also, weekly paclitaxel with its more metronomic dosing and better tolerability may provide additional advantages when combining it with novel immunomodulatory agents.

The historical rate of pathologic complete response (pCR) of TNBC to third generation anthracycline/taxane neoadjuvant chemotherapy is approximately 30%. Data from TNBC patients post neoadjuvant therapy demonstrated that those patients who attained a pathologic complete response had an excellent prognosis. The FDA recently has issued in its draft guidance a framework for the rapid introduction of novel agents for TNBC by using the pCR rate as a surrogate for accelerated approvals (with full approval contingent on long term follow up data showing benefit). Also, the recurrence pattern of TNBC is early (peak risk is 2-3 years from adjuvant therapy), so the follow up duration to see a difference in outcomes is shorter than it is for hormone receptor positive breast cancers. It is for

these reasons that this pilot study is being performed in the neoadjuvant setting for TNBC.(4, 5)

2.2. Study Agent

Talimogene laherparepvec (IMLYGIC™, formerly known as OncoVEXGM-CSF) (HSV-1 [strain JS1]/ICP34.5-/ICP47-/hGM-CSF) oncolytic immunotherapy is an immune-enhanced, oncolytic herpes simplex virus type 1 (HSV-1). In the talimogene laherparepvec strain, the HSV-1 viral genes encoding ICP34.5 (a neurovirulence factor) and ICP47 (which blocks viral antigen presentation to major histocompatibility complex [MHC] class I and II molecules) have been functionally deleted. In addition, deletion of the gene encoding ICP47 increases US11 expression, enhancing virus replication in cancer cells. The coding sequence for human granulocyte macrophage colony stimulating factor (GM-CSF) is inserted in place of ICP34.5, to enhance the immune response to tumor antigens released after virus replication. Thus, the intended therapeutic strategy is to produce a direct oncolytic effect by replication of the virus in the tumor, and induction of an anti-tumor immune response enhanced by the local expression of GM-CSF. The intended clinical effects include the destruction of injected tumors, the destruction of local, locoregional, and distant uninjected tumors, a reduction in the development of new metastases, a reduction in the rate of overall progression and of the relapse rate following the treatment of initially present disease, and prolonged overall survival.

Talimogene laherparepvec is administered by direct injection into tumors. Dose schedules may vary depending upon the tumor type and whether talimogene is administered as monotherapy or as part of combination therapy. For melanoma, an optimized 10^6 plaque forming units (PFU)/mL (total injected volume dependent on tumor burden) followed by subsequent doses of 10^8 PFU/mL is used. Optimum combination therapy regimens are still being evaluated. For melanoma and other indications currently under active development, an optimized dosing regimen consists of a first dose of 10^6 plaque forming units (PFU)/mL (total injected volume dependent on injectable tumor burden) followed by subsequent doses of 10^8 PFU/mL (total injected volume dependent on injectable tumor burden). 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 subjects. It is anticipated that this regimen will be used in most other oncology indications going forward, including talimogene laherparepvec in combination with other anti-cancer agents.

Talimogene laherparepvec 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 non-pathogenic virus with promising properties for cancer therapy. (6-12) BioVex has developed a clinical candidate virus with improved anti-tumor properties compared to previously available oncolytic viruses.

The modifications resulting in the enhanced properties of talimogene laherparepvec include the following:

- Use of a new isolate of HSV-1 (strain JS1) demonstrated in vitro to more effectively lyse a variety of human tumor cell lines than previous viruses used in clinical studies.(12-14)

- 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.(15-18)

- 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:

- 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.(9-11, 19, 20)

- 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 event between talimogene laherparepvec 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 talimogene laherparepvec 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 subjects treated to date.

Talimogene laherparepvec 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. Talimogene laherparepvec has been injected into normal and tumor-bearing mice to assess its safety. In general, the virus has been well tolerated, and doses up to 1 x 10^7 PFU/dose have given no indication of any safety concerns.

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

As of the 26 April 2018 data cutoff date for this investigator's brochure, clinical studies of talimogene laherparepvec have been or are being conducted in several advanced tumor types (advanced solid tumors, melanoma, head and neck squamous cell carcinoma [HNSCC], pancreatic cancer, and hepatocellular carcinoma). Cumulatively, an estimated total of 1253 subjects have received talimogene laherparepvec in clinical studies as of 26 April 2018. Key efficacy and safety results for talimogene laherparepvec are summarized in the investigator brochure.

Adverse event (AE): 86% were grade 1 or 2, but 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 talimogene laherparepvec related and occurred in two or more patients. Across all cohorts and severity grades, the most frequent AEs were consistent with CRT delivery. The grade 3 or 4 AEs observed in ≥2 patients were unrelated to talimogene laherparepvec. The adverse event profile, therefore, may include events related to talimogene laherparepvec, chemotherapy, radiation, tumor-related signs and symptoms, disease progression, and/or a combination of these. However, the concurrent use of talimogene laherparepvec, 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.(6) Overall, most adverse events reported in subjects administered talimogene laherparepvec are non-serious and primarily include flu-like symptoms and injection site reactions. Most fatal adverse events reported in

subjects administered talimogene laherparepvec were reported in the setting of disease progression.

After intratumoral injection, talimogene laherparepvec is generally cleared from subjects' blood and urine 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. A recent 20120324 study where pCR was used to detect TVEC 52% of the 60 subjects tested had positive DNA with injection site swabs. Of note however only 1% were positive in the TCID50 (viral infectivity assay). Overall, at any time point, a low percentage of subjects (13% [4/30]) had swabs that were positive for virus at the tumor site. In most cases, this was observed in seronegative subjects in the phase 1 study, in which a higher first dose of talimogene laherparepvec was administered than has been used in subsequent studies. Additional biodistribution and shedding data are currently being collected in Study 20120324. Talimogene laherparepvec DNA was detected with the lowest frequency in samples from the oral mucosa (1% of samples in 12% of subjects), the anogenital area (2% of samples in 15% of subjects, with almost all detected at a concentration below the lower limit of quantification of the assay), and from urine (3% of samples in 32% of subjects).

No cases of confirmed infection of non-tumor tissue by talimogene laherparepvec in treated patients have been reported to date. In the pivotal clinical study, adverse events related to HSV infections were reported in 5.5% (n = 16) of subjects in the talimogene laherparepvec group and 1.6% (n = 2) in the GM-CSF group. Most of the cases were reported as oral herpes and 1 case each was reported as herpes simplex and herpetic keratitis in the talimogene laherparepvec group. The subject 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 talimogene laherparepvec could not be confirmed as viral testing was not performed.(21) As talimogene laherparpvec is now FDA approved in the US as Imlygic for melanoma, the prescribing insert can be found at http://*pi.amgen.com/united_states/**imlygic/imlygic**_pi.pdf* and as an appendix to this protocol.

2.3. Other Agent(s)

The treatment for triple negative breast cancer is based upon cytotoxic chemotherapy, as there are no hormone receptors or HER-2 pathways upon which to direct therapy. However, there is no consensus standard of care treatment regimen for TNBC. Treatments are similar to those in hormone-receptor positive disease, including anthracyclines and taxanes, both of which increase disease free survival and overall survival when given in sequence. Doxorubicin given concomitantly with cyclophosphamide for four cycles has been shown to be equally as effective as cyclophosphamide, methotrexate, and 5-flourouracil over a six week cycle. CALGB 9344 demonstrated that the addition of four cycles of

paclitaxel following four cycles of AC increased disease free survival and overall survival.

The choice treatment and schedule used in this protocol is based upon the ECOG 1199, CALGB 9741, and SWOG 0221 trials. The ECOG trial compared four different taxane regimens to each other following dose-dense AC. These four regimens were paclitaxel given weekly for twelve weeks or every three weeks for four cycles or docetaxel given weekly for twelve weeks or every three weeks for four cycles. Of these taxane regimens, only paclitaxel given weekly was found to have a statistically significant five-year overall survival increase when compared to every 3 week paclitaxel (5-year OS: 89.7%). CALGB 9741 also compared 2x2, ultimately trying to determine conventional AC (every three weeks) vs dose-dense AC (every two weeks with G-CSF support) with doxorubicin and cyclophosphamide administered sequentially vs concurrently. Ultimately, an every two week (dose-dense) concurrent anthracycline based treatment was shown to be superior in terms of disease free survival, overall survival, and decreased risk of recurrence. Additionally, there were fewer instances of febrile neutropenia in the dose-dense concurrent arm, likely due to G-CSF supplementation. SWOG 0221 compared multiple arms for early stage breast cancer and recently reported on equivalent outcomes for the dose dense and weekly paclitaxel regimens.(1)

2.4. **Rationale**

Patients with triple negative breast cancer have a dichotomy of responses to treatment. Those patients who respond well to treatment and achieve complete pathological response are unlikely to have relapse of disease in five years. Patients who do not achieve complete response with neoadjuvant therapy are far more likely to have relapse in the first 2-3 years and die from their disease.

The goal of using talimogene laherparepvec is to achieve complete pathologic response in patients who may otherwise respond poorly to treatment. Previously conducted head and neck studies combining talimogene laherparepvec virus with cisplatin and radiation (standard therapy for squamous cell head and neck cancer) have shown complete response after treatment and no viable disease on neck dissection in 14 out of 15 patients.(6) By combining talimogene laherparepvec with standard neoadjuvant chemotherapy, the hope is for a similar response as seen in head and neck studies.

The goal of injecting talimogene laherparepvec directly into the tumor is to stimulate both systemic and local anti-tumor response. The insertion of a GM-CSF gene into the viral genome, as described in the previous section, will ideally create a humoral response within the tumor augmenting treatment and furthering the pathway to a complete response of the tumor.

3. **PATIENT SELECTION**

3.1. Eligibility Criteria

3.1.1. Patients must have histologically or cytologically confirmed clinical stage T2-3 N0-2 triple negative (estrogen receptor/progesterone receptor <1% HER2 0-1 by IHC or unamplified by FISH) invasive ductal carcinoma.

3.1.2. 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) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan. As well, patients must have primary tumor able to be visualized on ultrasound and amenable to direct injection.

3.1.3. No prior history of an invasive breast cancer

3.1.4. Adults ages: 18-70.

3.1.5. ECOG performance status 0-1 (Karnofsky ≥70%; see Appendix A).

3.1.6. Patients must have normal organ and marrow function as defined below:

-leukocytes	≥3,000/μL
-absolute neutrophil count	≥1,500/μL
-platelets	≥100,000/μL
-total bilirubin	within normal institutional limits
-AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
-creatinine	within normal institutional limits OR
-creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal
- MUGA Scan or ECHO	≥ EF of 50%

3.1.7. The effects of talimogene laherparepvec on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because the other therapeutic agents used in this trial are known to be teratogenic, sexually active women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.8. Ability to understand and the willingness to sign a written informed consent document.

3.2. Exclusion Criteria

3.2.1. T4 tumors, known metastatic disease, recurrent disease, inflammatory breast cancer, multicentric disease, and/or synchronous bilateral breast cancer

3.2.2. Patients with a second active malignancy, exceptions are localized non-melanoma skin cancers or prior in situ carcinoma

3.2.3. Patients receiving any other investigational agents or are unable to be treated with doxorubicin, cyclophosphamide, and paclitaxel.

3.2.4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to talimogene laherparepvec or other agents used in the study.

3.2.5. Patient with known active herpes simplex virus infections (prior uncomplicated oral HSV lesions are not an exclusion), prior complications from HSV infections such as encephalitis, or who require systemic antiviral therapy at the time of study enrollment should be excluded

3.2.6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, known active hepatitis B/C infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7. Patient on anticoagulation or with bleeding diathesis due to risk of hematomas at injection site

3.2.8. Pregnant or nursing women are excluded from this study

3.2.9. Immunocompromised patients may be at increased risk of herpetic infections when treated with talimogene laherparepvec. Therefore, HIV-positive patients, patients with acquired or congenital immunodeficiency conditions, those on chronic systemic immunosuppressants (requiring > 10mg of prednisone or equivalent/day),

3.2.10. Those with active autoimmune disease are excluded from the study.

3.2.11. Have received 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

3.3. **Inclusion of Women and Minorities**

Both men and women and members of all races and ethnic groups are eligible for this trial.

3.4. Patient Registration

Once clinical eligibility is confirmed, patients must sign an informed consent prior to registration indicating awareness of the investigation nature of the study and its inherent risks in keeping with the policies of the hospital and Federal regulations (Code of Federal Regulations Part 1X, Subpart B, Sections 50.20-50.27). The principal investigator in writing must approve request for an exemption to enroll a patient.

3.5. Removal of Patients From Study Treatment

- Patients may be removed from the study for any of the following reasons:
- Progression of disease
- Significant protocol violation
- Patient non-compliance: defined as any deviation from the protocol without prior agreement of the principal investigator
- Investigator non-compliance: defined as any significant medical or non-medical deviation from the protocol without agreement of the sponsor
- Patient's request to withdraw from the study or refusal of further therapy
- Herpetic infection requiring treatment with acyclovir or other similar anti-viral agent
- CTCAE grade 3 or above toxicity probably or definitely related to talimogene laherparepvec
- If patient does not meet eligibility criteria

3.6. Study early stopping criteria

For efficacy if 3 or fewer patients attain a pathologic complete response out of the first 12 patients enrolled on phase 2 enrollment will be halted. For safety, there is an interim safety analysis upon completion of phase 1 and the first stage of phase 2 (first 12 patients). If greater than 50% of patients experience a related G3-4 event that causes > 14 day delay in chemotherapy or premature cessation of chemotherapy enrollment will be halted.

4. TREATMENT PLAN

4.1. Study Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for talimogene laherparepvec and neoadjuvant therapy are described in Section 6. Appropriate dose modifications for talimogene laherparepvec and neoadjuvant therapy are described in Section 5. 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.

4.1.1. Talimogene laherparepvec

The first and second injections of talimogene laherparepvec will be injected 3 weeks apart (+/- 3 days) to allow for seroconversion, then the remaining injections will be given every 2 weeks (+/- 3 days) directly into the primary tumor only for up to five injections total concurrent with the paclitaxel treatments. The injections are not to be given during the doxorubicin/cyclophosphamide phase of neoadjuvant chemotherapy. This is done to avoid giving the injections during the more profound myelosuppression experienced during doxorubicin/cyclophosphamide and to allow eight weeks to elapse between the last injection and surgical resection of the primary lesion. This will minimize the risk of residual viral particles in the surgical site and significant pre-operative inflammation causing impaired wound healing. If there is no lesion visualized on ultrasound on a given injection day then no further talimogene laherparepvec should be injected and the remaining paclitaxel treatments should continue as planned.

Phase 1 treatment plan:

The phase 1 will use a 3+3 design with two dose levels of virus. For dose level one, patients will be enrolled and their treatment start dates staggered three weeks apart. Five weeks from the time the last patient in dose level one starts treatment must elapse before enrollment can commence for dose level two. If no DLTs are encountered in dose level one, then patients in dose level two can be enrolled and started concurrently, otherwise they too will be staggered three weeks apart. The paclitaxel weekly dose is fixed at 80mg/m2. The first dose level will utilize the 10^6 PFU dose vials for all five injections. The second dose level will use the 10^6 PFU dose vial for the first injection then the 10^8 PFU vials for the remaining four injections. The DLT evaluation period for dose escalation will be during the first five weeks (the first two injections). The MTD dose level is defined as the highest dose level with ≤1 out of 6 patients experiencing a DLT. This means if no DLTs are encountered in the first three patients enrolled in dose level one, then enrollment to dose level two should commence and six patients would be enrolled in dose level two. If the first dose level experiences two or more DLTs then accrual to the protocol will be held until discussions with the FDA, Amgen, and the protocol safety committee can be held to determine if any feasible amendments can be made to resume accrual. Accrual to the phase 2 expansion cohort will begin 5 weeks after the last phase 1 patient begins study therapy (completes the DLT evaluation period). A table is included with the 3+3 dose escalation rules.

Number of Patients with	**Escalation Decision Rule**

DLT at a Given Dose Level	
0 out of 3	Enroll next 3 patients at the next higher dose level.
$\geq$ 2 out of 3	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). If only three patients were enrolled at the previous dose level, then three more patients can be enrolled to the previous dose level (for a total of six). If six patients were already enrolled at the previous dose level then the previous dose level is the MTD.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, enroll 3 patients to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. If only three patients were enrolled at the previous dose level, then three more patients can be enrolled to the previous dose level (for a total of six). If six patients were already enrolled at the previous dose level then the previous dose level is the MTD.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is the MTD. At least 6 patients must be entered at this dose level in order to declare this.

A DLT is defined as the following:

Grade 3-4 toxicity probably or definitely related to talimogene laherparepvec which leads to chemotherapy treatment delays > 14 days or permanent cessation of neoadjuvant treatment with talimogene laherparepvec.

Any grade active herpetic infection events requiring oral acyclovir treatment which are related to TVEC administration.

Phase 2 treatment plan:

The MTD dose level will be used for all subsequent patients treated in the phase 2 portion of the study.

Dosing and administration of talimogene laherparepvec for phase 1 and 2:

The total volume of talimogene laherparepvec to be prepared will be based on investigator evaluation of injectable lesions and estimation of the total volume needed based on the talimogene laherparepvec Injection Volume Guideline Based on Tumor Size table.

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

The recommended volume of talimogene laherparepvec to be injected into the tumor is dependent on the size of the tumor on ultrasound on the day of injection and should be determined according to the injection volume guideline in the following table:

Talimogene Laherparepvec Injection Volume Guideline Based on Tumor Size

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

The following steps should be followed for drug administration:

Materials Inventory

- Laboratory coat, gloves and face shield, ISO gown,
- Dosing syringe for injection filled with talimogene laherparepvec
- 22 gauge needle with appropriate length selected for injection by physician (larger bore or spinal needles may be used if required for intralesional injection) Subsequent injections may need different gauge needle.
- Alcohol swabs
- Absorbent pad and dry occlusive dressing
- Injectable anesthetic as desired (i.e. lidocaine, benzocaine)
- Ultrasound probe covers

Lesion site preparation

- Talimogene laherparepvec will be injected intratumorally under US guidance with a radiologist and treating study physician. The radiologist will aid in localizing/directing the needle under US to the lesion. The needle will traverse the longest diameter of the tumor. Once in place the study physician will inject the virus into the tumor.
- Obtain three-dimensional measurements of the tumor by ultrasound and then indicate the appropriate volume of talimogene laherparepvec on the order form using the largest dimension, send to investigational pharmacy
- Swab the injection site and surrounding areas with alcohol, allow to dry
- The injection site/tract may be pre-treated with a topical anesthetic agent or an injectable local anesthetic; however, a local anesthetic must not be injected directly into the tumor

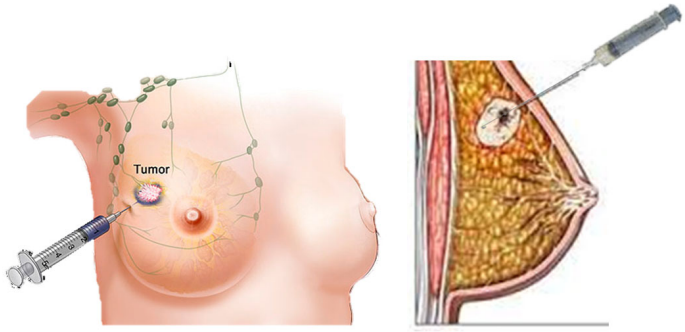
Lesion injection

- All personnel handling talimogene laherparepvec or material contaminated with talimogene laherparepvec must observe safety precautions (e.g., wear a laboratory coat, safety glasses and gloves)
- Inject talimogene laherparepvec intralesionally:

a) A single point of insertion will be used

b) Talimogene laherparepvec should be injected along the needle insertion track as the needle is withdrawn through the tumor. The needle will traverse the longest diameter of the tumor.

c) Distribute talimogene laherparepvec within the lesion through the insertion point using the reach of the needle to inject across the longest diameter. The preparation of talimogene laherparepvec will be injected while the needle is being pulled back from the furthest radial distance.



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

- Please ensure that gloves worn by the person administering the injection is discarded and a fresh pair of gloves is worn prior to proceeding to the next step.
- The injection site should be covered with a dry occlusive dressing Please ensure a fresh pair of gloves is worn when handling the dressing to prevent cross contamination with talimogene laherparepvec. Please also ensure that the outside of the dressing is wiped down with an alcohol swab to further minimize any cross contamination.
- Dispose materials used during injection (e.g., gloves, needles, gauze) in accordance with local/regional, BSL and institutional requirements for biohazardous waste (e.g. red biohazard bin)
- If the needle localization and injection is not successful, a second attempt will not be made. That injection will be omitted and the next attempt will occur according to study calendar.
- If the lesion is not penetrable with the needle selected, that injection will be omitted and the next attempt will occur according to study calendar.

Subject Counseling Information

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

4.1.2. **Neoadjuvant chemotherapy**

Patients will be administered intravenous neoadjuvant therapy consisting of paclitaxel 80mg/m2 weekly (every 7 days +/- 1 day) for 12 weeks followed by doxorubicin 60mg/m2 every 2 weeks for 8 weeks, and cyclophosphamide 600mg/m2 every 2 weeks for 8 weeks. Actual body weight dosing should be used to calculate dosing of chemotherapy agents. The neoadjuvant therapy should be administered whenever it is medically appropriate to do so, independent of whether the oncolytic virus injections can be given on schedule. In the event that solvent based paclitaxel is not

able to be given due to hypersensitivity reactions refractory to pre-medications, substitution with nab-paclitaxel at the same dose is allowable as per usual institutional guidelines if deemed appropriate by the treating physician.

4.1.3 **On treatment biopsy**

On week 6 of neoadjuvant therapy prior to injection of TVEC, patients will undergo an on treatment biopsy. The biopsy will be 2 14g cores placed into formalin for processing.

4.2. **Supportive Care Guidelines**

Additionally, the patients will receive pegfilgrastim subcutaneously 6mg to be administered 24 hours after each doxorubicin and cyclophosphamide infusion. Filgrastim may be given as required for neutropenia (ANC<1500) while on weekly paclitaxel on days 3-4 of each weekly cycle. All standard premedications and antiemetics for chemotherapy agents are allowed to be given (including dexamethasone). Premedication for paclitaxel should be 4mg of dexamethasone orally 30 minutes once prior to paclitaxel administration for the first two cycles. If no infusion reaction is experienced then dexamethasone can be omitted for the remaining paclitaxel cycles. If grade 1-2 infusion reaction is encountered during the first two cycles and can be successfully treated with using standard antihistamine doses (as indicated on the study treatment order) then the dexamethasone should be continued for all 12 paclitaxel cycles. Grade 3 or higher infusion reactions to paclitaxel would require discontinuation of the study treatment. Grade 1-2 allergic reactions or febrile states caused by talimogene laherparepvec cytokine release can be treated with antihistamines and/or acetaminophen as required. In the event any cellulitis is suspected in the breast then appropriate antibiotic therapy should be instituted immediately and further injections stopped until the infection has resolved.

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 talimogene laherparepvec (one time dexamethasone premedication during paclitaxel therapy is not excluded)
- 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

• 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.

4.3. **Duration of Therapy**

In the absence of treatment delays due to adverse events, treatment may continue for the full course of neoadjuvant chemotherapy or until one of the following criteria applies:

X Disease progression,

X Intercurrent illness that prevents further administration of treatment,

X Unacceptable adverse events(s),

X Patient decides to withdraw from the study, or

X General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5. DOSING DELAYS/DOSE MODIFICATIONS

5.1. **Talimogene laherparepvec**

If talimogene laherparepvec treatment was delayed due to adverse events or other reasons by > 1 week, that dose will be deemed to have been missed and the subject will proceed to the next scheduled treatment visit. If grade 2 or higher toxicities (CTCAE 4.0) that are probably or definitely related to the oncolytic virus occur, talimogene laherparepvec administration should be delayed until the adverse event has resolved completely. Dosing of talimogene laherparepvec should be delayed for active herpetic cutaneous or mucosal lesions, herpes labialis, antiviral therapy, grade 2 or higher immune related adverse event (irAE) (except vitiligo), ANC<1000, platelets < 50K, active cellulitis, skin breakdown, significant pain, or hemorrhage in the region of the injected tumor and/or affected breast. Resumption of the injections upon resolution is at the discretion of the treating physicians and investigators. Treatment with talimogene laherparepvec should be permanently discontinued in the event of a serious systemic herpetic

infection such as keratitis or encephalitis or grade 3 or 4 allergic reaction following injection. Patients with grade 1-2 allergic reactions can be pre-medicated using antihistamines.

There is no maximum allowable delay period that would automatically require complete cessation of the oncolytic therapy. If the condition of the patient returns to a state which is acceptable for resumption of injections and the patient is still undergoing therapy with weekly paclitaxel then any remaining injections can be given using the same dosing interval/schedule (i.e. a patient who had injection #2 held at week 4 of paclitaxel is cleared to get injections at week 6 then she can get three more injections at week 6, 8, and 10).

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

5.2. **Other Agent(s)**

Dose modifications and delays for chemotherapy would follow standard institutional guidelines and recommendations based on the prescribing information for each cytotoxic agent. The decision to administer the neoadjuvant chemotherapy is based solely on whether it is medically appropriate to give the chemotherapy dose and not dependent on whether the patient can receive a talimogene laherparepvec injection on any given day. Since neoadjuvant chemotherapy is given with curative intent, maximal dose intensity/density of the chemotherapy with appropriate supportive care should be administered whenever possible.

6. PHARMACEUTICAL INFORMATION

6.1. **Reported Adverse Events and Potential Risks for talimogene laherparepvec**

Identified Risk: Injection Site Reactions

Talimogene laherparepvec is administered by direct injection into cutaneous, subcutaneous, and nodal tumor masses. Injection site adverse events may occur, such as erythema, local skin discoloration, induration, warmth, and pain. Infrequently, injected cutaneous tumor masses may undergo necrosis, predisposing the subject to local and/or systemic infections. Similarly, injected pathologic lymph nodes may enlarge or become necrotic. Uncommonly, necrotic lymph nodes may be the site of persistent drainage that requires corrective measures. In clinical studies, adverse events of “injection site pain” and “injection site reaction” were very common, occurring in ≥ 10% of talimogene laherparepvec-treated subjects. Most events of injection site pain and injection site reaction in subjects receiving talimogene laherparepvec were mild to moderate in severity. Subjects seronegative at baseline for HSV-1, when given an

initial dose of talimogene laherparepvec at a concentration of 10^6 PFU, do not appear to experience more exaggerated injection site reactions than those who are seropositive at baseline.

Important Identified Risk: Accidental Exposure of Healthcare Providers (HCP) to Talimogene Laherparepvec

A needle stick injury, spill, or splash back during administration may result in accidental exposure of HCPs to talimogene laherparepvec. The ICP34.5 gene deletion is intended to allow only tumor selective replication and limited or no viral replication in normal tissues. However, talimogene laherparepvec injection can result in signs or symptoms of primary infection at the site of exposure.
A few reports of accidental exposure in study personnel have been received. In one of the cases, the exposed physician developed clinical signs/symptoms of a herpetic whitlow-like lesion at the site of the accidental needle stick injury that resolved without sequelae. An initial antibody assay was positive for an HSV-type virus. A confirmatory PCR assay was conducted 10 days after the accidental exposure and was positive for a virus with the ICP47 deletion, indicating that the virus was most likely talimogene laherparepvec. None of the other exposed individuals reported signs or symptoms of infection. In some cases oral acyclovir or valacyclovir was administered.

Important Identified Risk: Cellulitis at Site of Injection

Intralesional administration of talimogene laherparepvec by injection has been associated with cellulitis at the injection site. In some cases, a local inflammatory reaction with localized tumor necrosis developed, and in other cases, a bacterial infection developed. In the pivotal clinical study, the subject incidence of adverse events in the bacterial cellulitis category was 6.2% (n = 18) in the talimogene laherparepvec group and 1.6% (n = 2) in the GM-CSF group. The most frequently reported preferred term was cellulitis (5.8% in the talimogene laherparepvec group and 1.6% in the GM-CSF group). Seven subjects (2.4%) in the talimogene laherparepvec group and 1 subject (0.8%) in the GM-CSF group experienced serious adverse events of cellulitis. Fever, elevated white blood cell count, bacteremia or sepsis, and hospitalization for intravenous antibiotics were reported in 5 of the 7 cases in the talimogene laherparepvec group.

Important Identified Risk: Disseminated Herpetic Infection in Severely Immunocompromised Individuals

Patients with immunosuppression for any reason were excluded from clinical trials with talimogene laherparepvec. Disseminated herpetic infection in severely immunocompromised individuals is defined as an important identified risk based on the nonclinical data and literature described below. 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 talimogene laherparepvec 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

talimogene laherparepvec in Ewing's 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 talimogene laherparepvec treated SCID mice indicate that severe toxicity associated with disseminated viral infection may occur in patients who are severely immunosuppressed. The data in the BALB/c nude mice suggest the potential for toxicity due to talimogene laherparepvec 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 talimogene laherparepvec and HSV-1 viruses.

Important Potential Risk: Symptomatic Talimogene Laherparepvec Infection in Non-tumor Tissue in Treated Patients

Talimogene laherparepvec is a modified HSV-1 virus, and is engineered to replicate selectively in tumor tissue. However, if infection by talimogene laherparepvec of non-tumor tissue in treated patients were to occur, this could lead to development of clinical signs or symptoms that would be anticipated to be similar to signs or symptoms of wild-type herpes virus infection. In mouse tumor models, viral lysis/tissue injury was limited to tumors. No clinical or pathological evidence of symptomatic infection or injury to normal tissues was observed in nonclinical models dosed by repeated intratumoral, intravenous, or subcutaneous injection, including mice dosed with up to 10^7 PFU talimogene laherparepvec (~60-fold over the highest proposed clinical dose, on a PFU/kg basis) via weekly subcutaneous injection for up to 3 months. No cases of confirmed infection of non-tumor tissue by talimogene laherparepvec in treated patients have been reported to date. In the pivotal clinical study, adverse events related to HSV infections were reported in 5.5% (n = 16) of subjects in the talimogene laherparepvec group and 1.6% (n = 2) in the GM-CSF group. Most of the cases were reported as oral herpes and 1 case each was reported as herpes simplex and herpetic keratitis in the talimogene laherparepvec group. The subject 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 talimogene laherparepvec could not be confirmed as viral testing was not performed.

Important Potential Risk: Transmission of Talimogene Laherparepvec from Patient to Close Contacts or HCPs Via Direct Contact with Injected Lesions or Body Fluids (eg, Blood or Urine) Resulting in Symptomatic Infection (Primary or Reactivation)

Proximity of close contacts and HCPs to lesions in treated patients in the absence of effective barriers may result in the unintentional exposure of these individuals to talimogene laherparepvec. Exposure may occur via direct contact with injected lesions or via contact with body fluids (eg, blood or urine). The likelihood of transfer of talimogene laherparepvec to a close contact or HCP increases if the

contact has a break in the skin or mucous membranes. Signs or symptoms of infection would be anticipated to be similar to signs and symptoms of wild-type HSV infection.

Biodistribution by quantitative polymerase chain reaction (qPCR) testing in clinical studies indicated that low copy numbers of viral DNA were sporadically detected from 1hour to 1 week after intratumoral injection in blood and urine in 30% of subjects across all studies. Where subsequent samples were available, no viral DNA was detected at 2 weeks after injection. Shedding results showed that talimogene laherparepvec was detected on the surface of injected lesions for up to 2 weeks after injection in 8 of 72 (11%) subjects. Virus was not detected on the exterior surface of tumor dressings at any time point tested.

Biodistribution was evaluated after single and multiple dosing by intravenous, subcutaneous or intratumoral injection in mice. Doses from 1 x 105 to 1 x 107 PFU/mL were evaluated (0.6 to 60-fold higher compared to the maximum clinical dose). Across the studies, viral DNA was found most commonly at the site of injection regardless of administration route, which in the case of the tumor may reflect viral replication following intratumoral administration. Following intravenous administration of talimogene laherparepvec, viral DNA was detected in blood of 5 of 6 animals through 56 days of dosing. After intratumoral injection, talimogene laherparepvec DNA was detected by PCR in tumor, blood, in tissues associated with immune related viral clearance (lymph nodes, spleen), and tissues with high blood perfusion (heart, lung, liver). Viral DNA was found in the brain in 2 of 91 samples collected. Viral DNA was not detected in bone marrow, eyes, lachrymal glands, nasal mucosa or feces at any time point. Following intratumoral injection, viral DNA was cleared from the blood of most animals within 2 weeks postdose and in all animals by 6 weeks after the last dose. Following subcutaneous dosing, viral DNA was excreted in urine in 22% of animals within 24 hours postdose and all were negative at 4 weeks postdose.

<u>Important Potential Risk: Symptomatic Herpetic Infection Due to Latency and Reactivation of Talimogene Laherparepvec or Wild-type HSV-1 in Patients</u>
Infection of tumor or non-tumor tissue could potentially lead to the establishment of latency and subsequent reactivation of talimogene laherparepvec if the virus came into contact with axonal nerve terminals and was transported to neuronal cell bodies. The genetic modifications made to talimogene laherparepvec do not prevent the virus from entering latency or subsequently reactivating. However, HSV-1 strains deficient in the ICP34.5 gene are unable to replicate efficiently in non-tumor cells, including neurons, and are impaired for establishment and reactivation from latency when compared to wild-type HSV-1 (Chou et al, 1990; Perng et al, 1995; Perng et al, 1996, Robertson et al, 1992; Spivack et al, 1995). Thus, reactivated virus in nerve cells is expected to be less likely to lead to clinical signs or symptoms as compared to wild-type HSV-1. Co-infection of neurons already harbouring latent wild-type HSV-1 by talimogene laherparepvec could potentially stimulate the reactivation of latent wild-type HSV-1 in patients

with prior infection. A febrile response associated with injection of talimogene laherparepvec might stimulate reactivation of wild-type HSV-1 in patients with prior exposure and latent HSV-1 infection.

Biodistribution studies in mice have detected low levels of talimogene laherparepvec in trigeminal ganglia (at levels 0.2-1.2% found in concurrent blood) through 28 days in 1 of 6 animals following high dose intravenous administration (0.6 × 107 PFU, ~36-fold over the highest proposed clinical dose). Talimogene laherparepvec was undetectable in trigeminal ganglia in mice after subcutaneous administration.

In a mouse model, talimogene laherparepvec was detected in the spinal dorsal root ganglia following injection into the foot. This suggests the virus had established latency in the nerve root innervating the site of injection. The virus was reactivated in ex vivo cell culture. The clinical applicability of these findings is not certain, as it is anticipated that host immunity will respond to protect the host from talimogene laherparepvec replication in non-tumor tissue in individuals with an intact immune system.

Important Potential Risk: Immune-mediated Adverse Events
Based on review of adverse events suggestive of an immune-mediated etiology across melanoma studies, immune-mediated adverse events considered possibly related to talimogene laherparepvec were reported in 2% of subjects treated with talimogene laherparepvec, and included events of vasculitis, glomerulonephritis, acute renal failure, pneumonitis, and worsening psoriasis. Other contributory factors were identified in several of these cases, including pre-existing immune-mediated conditions, other concurrent medications, or intercurrent medical events.

Important Potential Risk: Talimogene Laherparepvec-mediated Anti-GM-CSF Antibody Response
There is a theoretical concern that transgene-derived expression of GM-CSF could induce an immune response reactive with endogenous GM-CSF. Antibodies against GM-CSF have been detected sporadically in the general population (up to 9.6%) (Meager et al, 1999). Case reports of cryptococcal meningitis and pulmonary alveolar proteinosis have been reported in association with auto-antibodies to GM-CSF (Rosen et al, 2013). Auto antibodies to GM-CSF were demonstrated to reproduce the disease of pulmonary alveolar proteinosis in nonhuman primates (Trapnell et al, 2009). It is not known whether such phenomena could be expected with the limited exposure anticipated with transgene expression of GM-CSF from talimogene laherparepvec.

Important Potential Risk: Plasma Cell Dyscrasia (Plasmacytoma) at the Injection Site
A plasmacytoma was reported in 1 subject treated with talimogene laherparepvec in the pivotal clinical study. A plasmacytoma developed in the area of the injected tumor on the scalp after 9 cycles of treatment with talimogene

laherparepvec. Study treatment was permanently discontinued. On medical review, the event was determined likely to be a secondary plasmacytoma which developed at the injection site due to recruitment of plasma cells in response to the talimogene laherparepvec injections in a subject who had a pre-existing (smoldering) multiple myeloma.

Important Potential Risk: Impaired Wound Healing at Site of Injection
The local tissue response following repeated injections of a foreign protein can contribute to chronic inflammation, necrosis, and ulceration of tumor sites, and in the presence of other risk factors, delayed healing may result. In the pivotal clinical study, the incidence of adverse events in the impaired wound healing category was 5.5% (n = 16) in the talimogene laherparepvec group and 2.4% (n = 3) in the GM-CSF group. Wound complication, wound secretion, and wound infection were reported in ≥ 1% of subjects in the talimogene laherparepvec group. A serious adverse event of impaired healing was reported in an elderly subject following treatment with talimogene laherparepvec to a recurrent lower extremity melanoma lesion that resulted in a below the knee amputation 7 months after the last treatment. The subject had a history of peripheral vascular disease, prior radiation at the site of injection, and recurrent cellulitis in the area, all which were considered possible contributory factors.

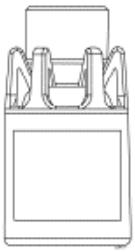
Important Potential Risk: Disseminated Herpetic Infection in Individuals with Deficiency in Cell-mediated Immunity Such as Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS), Lymphoma, or Leukemia, or Who Require High Dose Steroids or Other Immunosuppressive Treatments Such as Post Organ Transplant
Talimogene laherparepvec is a recombinant replication-competent HSV-1 type virus which is engineered to replicate selectively in tumor cells. Intratumoral injection of talimogene laherparepvec was 100% lethal in SCID mice (SCID model) and in up to 20% of athymic mice (nude mouse model). Refer to the characterization of the important identified risk of "disseminated herpetic infection in severely immunocompromised individuals" for a description of results of nonclinical studies in SCID mice and BALB/c nude mice. The clinical relevance of these data to patients treated with talimogene laherparepvec is not clear. Wild-type HSV-1 infection in immunocompromised individuals is associated with dissemination of the virus and serious, life-threatening toxicity. Patients with immunosuppression were excluded from clinical trials with talimogene laherparepvec. The potential risk and potential benefits of treatment of patients with HIV/AIDS, leukemia, lymphoma, or patients who require treatment with chronic high dose steroids or other immunosuppressive agents such as those used in the post transplant setting should be considered prior to treatment. Talimogene laherparepvec is contraindicated in patients with severe immunodeficiency.

Important Potential Risk: Arterial bleeding (Carotid Artery Blowout Syndrome) has been reported following administration of talimogene laherparepvec in the

setting of recurrent squamous cell carcinoma of the head and neck (SCCHN). Subjects with tumors in direct contact or encasing a major blood vessel with ulceration and/or fungation into the skin surface, and subjects with a history of re-irradiation for SCCHN or prior lymph node neck dissection to a field which involves the carotid arteries may be at increased risk for arterial hemorrhage if talimogene laherparepvec is injected into tumors near major blood vessels. Such high risk subjects should not be administered talimogene laherparepvec in the SCCHN setting. Consider the risks and benefits of treatment before administering talimogene laherparepvec to these subjects.

6.2. **Talimogene laherparepvec description**

Talimogene laherparepvec will be presented as a sterile, semi-translucent to opaque solution for injection (opacity is different for each concentration) preservative-free frozen liquid in a single use 2 mL cyclic olefin polymer (COP) plastic resin vial. Each vial will contain talimogene laherparepvec at a nominal concentration of 10^6 PFU/mL or 10^8 PFU/mL in an aqueous sodium phosphate buffer with sodium chloride, sorbitol and myo-inositol added as stabilizers and water for injection (WFI). Vials are appropriately filled to ensure that a sufficient deliverable dose is provided. Each 2 mL vial will contain approximately 1.15 mL of talimogene laherparepvec with a 1.0 mL deliverable volume. Each vial is intended for single use only and will be available in one of two different presentations:

Current supplies of talimogene laherparepvec is provided as a preservative-free solution in a single–use vial without a clear copolyester plastic sleeve. The product label is found on the vial itself	Future supplies of talimogene laherparepvec will be provided as a preservative-free solution in a single–use vial permanently inserted into a clear copolyester plastic sleeve. The product label will be found on the vial sleeve
	
	Note that the Closed System Transfer Device (CSTD) tested for use with the vial sleeve is the PhaSeal CSTD

Vials will be sealed with gray rubber stoppers, Fluoropolymer-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. The supply for 10^6 PFU/mL vials will be packaged separately from the supply for the 10^8 PFU/mL vials.

- The 10^6 PFU/mL strength is supplied in a box containing 10 vials.
- The 10^8 PFU/mL strength is supplied in a box containing 20 vials.

The dimensions of the box (of both strengths) are approximately 12.7 x 12.7 x 5 cm (4.891 in. x 4.891 in. x 1.969 inches). Due to the temperature at which talimogene laherparepvec packaging occurs no tamper-evident seal or closure seal will appear on the boxes. Talimogene laherparepvec is sensitive to light and should be protected from light during storage.

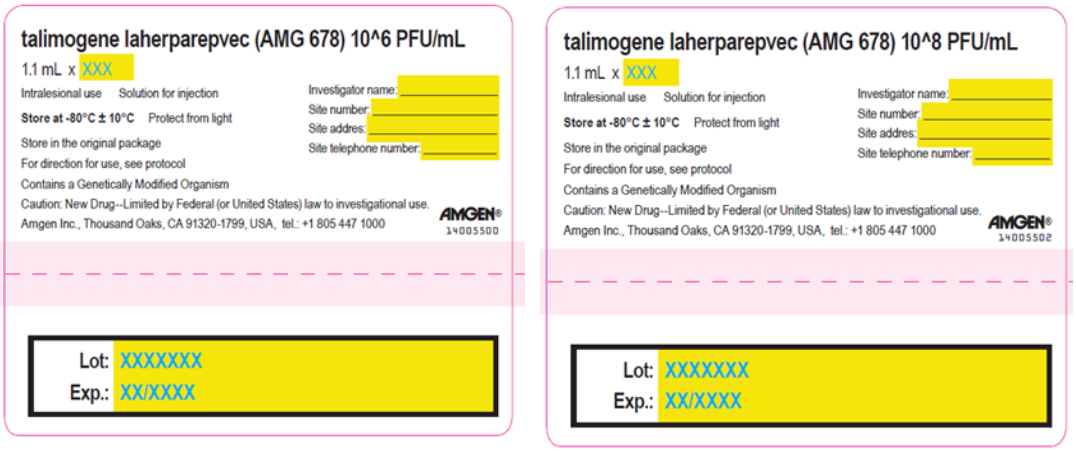
Product Labels for Investigational Product

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

Figure 1 - Examples of Product Labels (talimogene laherparepvec):

Examples of Vial Labels (talimogene laherparepvec):

Examples of Carton Labels (talimogene laherparepvec):



Please note:
• For vials supplied inserted into the vial sleeve, there may be a label attached to the vial in addition to a label on the outer sleeve. The label on the plastic sleeve is the study label and content on the vial label should be disregarded.
• The lot number printed on the Talimogene laherparepvec vials is the Labeled Drug Product (LDP) lot.
• The lot number printed on the box label is the Finished Drug Product (FDP) lot number.

Receipt and Storage of Investigational Product

Talimogene laherparepvec is shipped frozen by air courier or truck transit in an approved shipper suitable for biological substance shipments. The shipper will contain talimogene laherparepvec vials within their secondary packaging on dry ice. The shipment will also contain two (2) TempTale data loggers, unpacking instructions, as well as all shipment related documentation which must be completed and returned to Amgen and/or filed at site as per the instructions on the relevant documentation.

Shipping
Talimogene laherparepvec is shipped frozen by air courier or truck transit in an approved shipper suitable for biological substance shipments. The shipper will contain talimogene laherparepvec vials within their secondary packaging on dry ice. The shipment will also contain two (2) TempTale data loggers, unpacking instructions, as well as all shipment related documentation which must be completed and returned to Amgen and/or filed at site as per the instructions on the relevant documentation.

Initial supply requirements
Initial drug supplies will be sent to the site once the site has been activated by Amgen Distribution and the Drug Request Form has been received by Amgen. Please allow one (1) business day to process the Drug Request Form. Domestic or Canadian express shipments may take up to two (2) days transit time. Therefore, a total turnaround time for drug supply requests is expected to be three

(3) days.

Resupply requirements

Resupply of product(s) will occur once a Drug Shipment Request form is completed by the site and submitted to Amgen as per the details required on the form. Re-supply will be made according to details provided on the Drug Shipment Request form.

Receipt

To ensure the stability of talimogene laherparepvec, vials must be received, unpacked and placed into storage **within 90 seconds**. Detailed unpacking instructions are provided in each shipment. The pharmacy team should have a plan of action to allow for quick and efficient transfer of the box of vials into the freezer (for example, by placing the shipper box close to the freezer before opening the shipper box and completing the next steps of the process). Clinical trial sites are encouraged to review these instructions prior to receipt of clinical trial materials.

Storage

To ensure stability and quality are maintained, the product must be stored correctly upon receipt and for the duration of the study under the conditions specified below.

Talimogene laherparepvec must be stored in a non-cycling freezer maintained at a set point of -80ºC in a secured location until planned use. Cycling, frost-free, auto defrost freezers must not be used since they cycle to warmer temperatures several times a day. Vials should be kept within the secondary container to protect from light.

Storage of Talimogene Laherparepvec - Freezer Set Point

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

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

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

Destruction of Product at Site

All used and unused (including expired) Investigational Product supplied by Amgen must be destroyed locally, following local capabilities and regulatory requirements. Applicable product reconciled must be completed before destruction can occur. Where available, place relevant local certificates of destruction in the appropriate section of the pharmacy file. Imlygic (talimogene laherparepvec) has been defined as a GMO. Please ensure all country/local regulations for destruction are followed.

Transfer and/or Transportation of Investigational Product

Transfer of talimogene laherparepvec 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.

Drug Preparation and Administration Location

Talimogene laherparepvec is open-label bulk supply that can be used across study subjects. Talimogene laherparepvec is supplied in two concentrations. For US sites, the talimogene laherparepvec Safety Data Sheet categorizes the drug as a Biosafety Level (BSL) 1, thus use of BSL 1 containment procedures is recommended.

Unless otherwise directed by local regulations:

- The use of a microbiological safety cabinet or hood for the dose preparation of talimogene laherparepvec is not required.
- Talimogene laherparepvec may be safely drawn up into syringes in the room used for product administration, although this may also optionally occur elsewhere (eg, in the pharmacy).
- Any side room away from other subjects can be used for talimogene laherparepvec administration.

Materials Inventory

- Sterile disposable needle to withdraw talimogene laherparepvec from vials
- Sterile 22-24 gauge needle for injections
- Sterile 1 mL to 5 mL syringe, based on injection strategy
- Laboratory coat, gloves and safety glasses
- Alcohol swabs

Thawing of Frozen Vials

To ensure proper usage of talimogene laherparepvec, the following instructions have been developed.

- All personnel handling the talimogene laherparepvec or material contaminated with talimogene laherparepvec must observe safety precautions (e.g., wear a laboratory coat, safety glasses and gloves)
- Determine which box labeled with the appropriate concentration, 10^6 PFU/mL or 10^8 PFU/mL, is to be prepared
- Remove the number of frozen vials from the box that have been calculated for administration and immediately (**within 90 seconds**) return the remaining vials to the freezer. Care should be taken to avoid unintended thawing of vials that will not be used. The time the vials are removed from the freezer must be recorded.
- Thaw frozen vials until liquid at **room temperature** [59°F to 86°F (15°C to 30°C)]. Thaw should take approximately 30 minutes. Please ensure vial is

protected from light during the thaw process, using the original carton or a light protective bag (with adequate space, approximately 2.5cm between each vial).

During the thaw:

- Leave vials undisturbed, except to gently swirl to check for completion of thaw
- Never shake vials vigorously, especially during the thawing process

After the thaw:

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

Preparation of Dosing Syringe for Injection

- All personnel handling talimogene laherparepvec or material contaminated with talimogene laherparepvec must observe safety precautions (e.g., wear a laboratory coat, safety glasses and gloves)
- Talimogene laherparepvec dosing syringe must be properly labeled in accordance with current ICH GCP and local/regional or BSL requirements prior to dispensing for administration
- Clean talimogene laherparepvec vial stopper with an alcohol swab
- Withdraw appropriate volume of talimogene laherparepvec required with the appropriate number of sterile syringes and needles
- Remove the needle used to withdraw the talimogene laherparepvec from the vial and attach a sterile 22-24 gauge needle suitable for intralesional injection
- Please refer below for the Clinical Handling Timelines. Discard any prepared syringes not used for administration within the specific times stated.
- Discard materials used in the preparation (e.g. gloves, needles) in accordance with local/regional or BSL classification guidelines.

Clinical Handling Times Outside Labelled Storage Conditions

General product handling considerations
Thaw • **Thaw frozen talimogene laherparepvec vials at 15°C to 30°C (59°F to 86°F) protected from light until fully liquid (approx. 30 minutes at the stated temperature range). Do not expose vials to higher temperatures.** • **Swirl gently. Do not shake.** • **Do not refreeze thawed talimogene laherparepvec.** **Storage and Preparation**

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

Administration

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

Total storage time for thawed 10^6 PFU/mL product

2°C to 8°C (36°F to 46°F)	**up to 27°C (80°F)***
12 hours (inclusive of 4 hours maximum in the syringe)	4 hours (inclusive of 2 hours maximum in the syringe)

Total storage time for thawed 10^8 PFU/mL product

2°C to 8°C (36°F to 46°F)	**up to 27°C (80°F)***
48 hours (inclusive of 8 hours maximum in the syringe)	4 hours (inclusive of 4 hours maximum in the syringe)

Agent Accountability

The Investigator, or a responsible party designated by the Investigator in the investigational pharmacy, must maintain a careful record of the inventory and disposition of all agents received from Amgen.

6.3 Commercial Agent(s)

Please refer to package insert for doxorubicin, cyclophosphamide, and paclitaxel for dosage forms, ingredients, solution preparation, and route of administration. Also refer to package insert for adverse events and safety information. Commercially available stocks will be used.

6.4 Temperature Monitoring

Temperature monitoring of the storage temperatures, via a manual or electronic temperature log, of all locations where talimogene laherparepvec is stored is

required. Actual temperature, plus range of temperatures (minimum/maximum), must be documented.

Due to the temperature sensitivity of talimogene laherparepvec, the chosen device specifications should be checked carefully to ensure the device covers the specified temperature ranges required. Temperature monitoring equipment should be serviced and calibrated in accordance with the manufacturer's guidelines and/or institutional policies.

Freezer and refrigeration units used to store Product should be properly maintained (in accordance with manufacturer's instructions).

Temperature excursions described in this section apply only to frozen product in storage. Vials that are removed from storage, thawed and prepared for patient administration should be monitored according to the guidelines provided per Clinical Handling Timelines.

Temperature Excursion – Definitions, Reporting and Management

A temperature excursion (TE) occurs when a Product is exposed to temperatures outside of its recommended storage range.

The following rounding rules described below should be applied in all cases: For example, a reading of -69.4°C would be rounded to -69°C and -90.5°C would be rounded to -91°C. These would be considered temperature excursions. Alternatively, a temperature of -69.5°C would be rounded to -70°C and -90.4°C would be rounded to -90°C. These would NOT be considered temperature excursions.

Reporting Temperature Excursions

Sites will report temperature excursions according to the instructions provided.

Frozen Storage Temperature Excursion Limits

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

Note: For temperature requirements during clinical handling/ IP preparation, refer to Clinical Handling Timelines.

Temperatures colder than -90°C and warmer than -45°C

- Sites must report the excursion using the Investigator Sponsored Studies (ISS) Temperature Excursion Submission ensuring that all details on the form are completed fully and accurately. This includes details of the exposure time of the IP at the various temperature ranges.

- Send a copy of the completed form to the email address listed at the bottom of the form and file the original form in the relevant section of the Pharmacy File.

Temperatures within the range -69°C to -45°C:

- Sites should record each event within this range on the Temperature Excursion Tracking Log and following the instructions that accompany the form. Each consignment should have a separate Tracking Log, as each shipment will need to be tracked separately.

- Cumulative duration time of the temperature excursions within this range should be captured.

- Once a cumulative period of 1512 hours has been reached, the site should submit the ISS Temperature Excursion Submission Form making sure all relevant details on the form are completed fully and accurately. (Important: Consider IP shipment timeframes when tracking TEs and order replacement stock in a timely manner).

- Send a copy to the email address listed at the bottom of the form, and file the completed Temperature Excursion Submission Form(s) in the relevant section of the Pharmacy File.

Temperature excursions of prepared IP, outside the Clinical Handling Timelines, should be documented but are not reportable as temperature excursions. Instead, the affected products should be considered unfit for use and should be destroyed by the site.

Management of Product(s) Exposed to a Suspected Temperature Excursion

Under no circumstances should any product impacted by an actual or suspected temperature excursion be administered to or by subjects before a temperature excursion assessment is completed by Amgen. Pending such an assessment, all product(s) suspected of being exposed to a temperature excursion should be quarantined under the appropriate storage conditions.

Affected product should only be removed from quarantine when:

- The excursion assessment has determined the product is suitable for use. In this case, the product can be removed from quarantine for continued use.
- The excursion assessment has determined the product is NOT suitable for

use. In this case, the product must be returned/destroyed according to institutional/site policies.

Temperature Excursion Assessment by Amgen

Amgen will provide written notification/instructions via a Product Impact Memo for each evaluated temperature excursion. If subjects are currently on-study and receiving Product(s), review the next expected dosing visit to determine if immediate re-supply is required, then complete and submit the Drug Shipment Request form accordingly. Suspect Product(s) must not be administered to subjects until deemed acceptable by Amgen.

7. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done within 4 weeks prior to the start of therapy. 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. Informed consent can be obtained within 28 days prior to treatment start.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13-21 q2 wks	Off Study[c]
Talimogene laherparepvec [A]		X			X		X		X		X				
Doxorubicin [B]														X	
Cyclophosphamide [B]														X	
Paclitaxel [B]		X	X	X	X	X	X	X	X	X	X	X	X		
Informed consent	X														
Demographics	X														
Medial History	X														
Concurrent meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X	X			X		X		X		X			X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X														
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance Status	X	X			X		X		X		X			X	X
CBC w/ diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry [a]	X	X			X		X		X		X			X	X
Anti HSV Ab	X						X								
MUGA or ECHO + EKG	X														
Adverse Event Evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tumor Measurements	X	Tumor measurements by exam (if palpable) are repeated every study visit.													X[c]
Radiologic evaluation [d]	X[d]	US measurements should be performed while getting talimogene laherparepvec injections													X[c]
B-HCG	X[b]														
Tumor IHC for T cells	X						X[f]								X
Immunohistochemistry of lymph nodes	X														X
Blood sampling for biomarkers[e]	X		X			X				X					

A: Talimogene laherparepvec: Dose as assigned; administration schedule(only if tumor is visualized on US) (+/- 2 day window for scheduling issues)

B: Paclitaxel 80mg/m2 IV weekly (+/- 1 day window for scheduling issues) x 12 followed by doxorubicin 60mg/m2 + cyclophosphamide 600mg/m2 IV q2 weeks x 4

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

b: Serum pregnancy test (women of childbearing potential).

c: Off-study treatment evaluation should be completed within 30 days after last chemotherapy treatment. Patients will continue to be followed up post op to determine degree of pathologic response, note any perioperative complications, and also will be followed every 6 months (+/- 1 month) for 5 years by telephone, review of follow up notes for recurrence status and latent herpetic infection. See section below for details.

d. In addition to US, patients should get baseline staging scans (CT thorax/abd w/ contrast and bone scan or PET) when clinically indicated to rule out metastatic disease. If staging imaging is not clinically indicated it is not required. See section below for details.

e. blood sampling must be collection prior to drug administration

f. to be collected prior to the week 6 treatment

Prestudy procedures evaluation:

Informed consent, demographics, concominant meds, performance status, physical exam, vitals, height, weight, complete blood count, complete metabolic panel, serum pregnancy test, serum HSV1 Ab, EKG, tumor measurement by palpation/exam, blood sampling for biomarker testing request slides from tumor and lymph node (if done) biopsies for IHC analysis. Prestudy procedures can be completed same day as day 1 treatment if necessary.

Radiologic scans/imaging including the US, MUGA/ECHO, staging scans (CT + bone scans or PET/CT) as clinically warranted for neoadjuvant patients per NCCN guidelines (stage 2B node positive or stage III patients, not stage I or IIA node negative patients with no signs/symptoms suspicious for metastatic disease) are done within 4 weeks of 1st study treatment day.

Weeks 1,4,6,8,10 procedures:

Complete blood count, complete metabolic panel, US measurement for dosing of talimogene laherparepvec, pharmacy to begin thawing/preparation of dose, clinic visit with concurrent meds, performance status, physical exam, vitals, weight, tumor measurement by palpation/exam, then US for injection localization into tumor, injection of talimogene laherparepvec into primary tumor (+/- 3 days around the scheduled paclitaxel administration day), administration of weekly paclitaxel dose (6-8 days from last paclitaxel dose for weeks 4,6,8,10). The talimogene laherparepvec can be given either before or after the paclitaxel depending on scheduling/readiness of radiology/pharmacy on the treatment day. Ideally all treatments are given on the same day but if scheduling doesn't permit then the grace periods specified above can be used to stagger the paclitaxel and talimogene laherparepvec on different days (with the study clinic visit and safety labs done on the paclitaxel infusion day scheduled for that week) when required due to circumstances. A biopsy will be collected on week 6 prior to initiating treatment with talimogene laherparepvec.

Weeks 2,3,5,7,9,11,12 procedures:
Complete blood count, vitals, weight, administration of weekly paclitaxel dose (6-8 days from last paclitaxel dose). Blood for biomarker sampling will be collected pre-dose week 2, 5, and 9.

Weeks 13 -21 procedures:
Complete blood count, complete metabolic panel, clinic visit with concurrent meds, performance status, physical exam, vitals, weight, tumor measurement by palpation/exam every 2 weeks (+/- 1 day) x 4 on the same day as administration of standard of care dose dense doxorubicin/cyclophosphamide chemotherapy.

Off study procedures:
Complete blood count, complete metabolic panel, clinic visit with concurrent meds, performance status, physical exam, vitals, weight, 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 post last study treatment. Data on any perioperative complications should be collected as well. Final tumor measurement/assessment will be done based on the post-operative pathology report

when available in the EMR 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 5 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. Long term follow up schedule will continue until 5 years after the off study visit date, death, or patient is lost to follow up whichever occurs first.

8. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be reevaluated for response every two weeks (with the exception of the 3 week interval between injection #1 and #2 which is three weeks) using physical exam and ultrasound (until the injections are completed or tumor is no longer visualized whichever occurs first). In addition the patient's response will be evaluated by a pathologist following surgical excision.

8.1. Definitions

Pathologic complete response

Response and progression will be evaluated in this study using a primary endpoint of pathologic complete response defined as absence of residual invasive adenocarcinoma in the breast and ipsilateral lymph nodes (ypT0/isN0) following completion of all neoadjuvant systemic therapy. Other endpoints looking at rate of breast only pathologic complete response rate will be evaluated.

8.2. 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 easily palpable or not present then it should be noted as such in the patient note.

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. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical measurement of palpable lesions: This evaluation is primarily for assessing how the patient is responding overall to the therapy and ensuring that there is no evidence of clinical progression during treatment that would require referral back to the patient's surgical team for resection.

Ultrasound (US) should be used for localization of the lesion/clip, guide injections,

determine dosing, and measurement of the primary lesion. Measurement should be tri dimensional and recorded on each ultrasound procedure note in the medical record. Lesions that are not visualized following the initiation of therapy should be noted as such.

8.3. Response Criteria

8.3.1. Evaluation of primary lesions

Complete Response (pCR):	Disappearance of histopathologic evidence of malignant cells in breast and axillary lymph nodes
Partial Response (pPR):	Evidence of residual invasive malignant cells in breast and/or axillary lymph nodes
Progressive Disease (PD):	Increase in size of primary lesion or axillary lymphadenopathy since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	No change in histopathologic examination of breast and axillary lymph nodes without increase in size or number of lesion(s).

8.4. Follow up evaluation

8.4.1. Pathologic evaluation

Pathologic evaluation for post neoadjuvant therapy residual disease will be made upon completion of all neoadjuvant systemic therapy on the resected surgical specimen(s) and a synoptic pathology report will be generated per standard institutional practice. The ypTN staging information, presence of treatment effect in the tumor bed and any resected lymph nodes, estimated tumor volume reduction should be recorded in Oncore case report forms.

8.4.2. Duration of follow up for patient outcomes

Follow up of any treatment related adverse events until resolution, stabilization, or death for a minimum of 30 days post last study treatment. Data on any perioperative complications should be collected as well. Final tumor measurement/assessment will be done based on the post-operative pathology report when available in the EMR 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 5 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.

8.5. **Response Review**

Pathology will be reviewed for response by Moffitt Cancer Center pathologists.

9. REGULATORY AND REPORTING REQUIREMENTS

This protocol is associated with an Investigational New Drug Application ("IND") sponsored by either Moffitt Cancer Center or an Investigator. IND Safety Reports are required for any adverse experience associated (or possibly associated) with the use of the investigational product(s) that is both serious and unexpected. To meet the IND Safety Reporting requirements set forth in 21 CFR §312.32, FDA Form 3500A (MedWatch form) will be completed and provided to the Moffitt Office of Institutional Regulatory Affairs for Investigational Drugs and Devices.

9.1. **Reporting Adverse Events**

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 of the adverse event to the study drug or standard of care chemotherapy, with final approval within ten 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 five 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 within30 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. All SAEs will be reported to the Clinical Trial Office of Moffitt Cancer Center in 24 hours via Oncore. Serious adverse events will be reported to the IRB according to IRB policy. This includes new herpetic infections in talimogene laherparepvec treated patients or their close contacts (see section 7 under long term follow up) 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.

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

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.

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 anybody governing research conduct (e.g., RA, IRB, etc.)
Final (End of Study) Report, including: • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	At time of ISS sponsor submission to any body governing research conduct (e.g., RA, IRB, etc.) but not later than 1 calendar year after study completion

Accidental Exposures to Talimogene Laherparepvec and Herpetic Event

Reporting

In order to better assess and understand the potential risks to treated patients and/or third parties following the treatment of clinical trial subjects with talimogene laherparepvec, special reporting procedures apply for accidental exposures to talimogene laherparepvec and for suspected herpetic events. See Table 3 for a summary of reporting requirements. Clinicians should review the Imlygic package insert (available online) for additional information on the safe handling of talimogene laherparepvec.

Accidental Exposure of HCPs to Talimogene Laherparepvec

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

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

9.3. Interim analyses

Safety interim analysis: The safety data will be analyzed upon completion of the phase 1 and also after the first twelve phase 2 patients have been treated. At either point, if greater than half of the treated patients experience a G3-4 toxicity related to talimogene laherparepvec which leads to chemotherapy treatment delays > 14 days or unplanned cessation of neoadjuvant treatment then accrual to the trial will be held until discussions with the sponsor and protocol monitoring committee are arranged to

determine if accrual can resume. Any deaths on study treatment should trigger an immediate safety review and accrual hold until the event is fully investigated and a determination is made by the PI, study sponsor and protocol monitoring committee.

10. **STATISTICAL CONSIDERATIONS**

10.1. **Study Design/Endpoints**

Phase 1 design:
The phase one portion of the study uses a standard 3+3 design with the primary endpoints being safety/toxicity described using CTCAE 4.03 criteria and the MTD. Descriptive statistics including frequency of adverse events, number of treatments administered as planned, and patient demographics will be reported in tabular form. Patients receiving any study treatment will be evaluable for the safety endpoint.

The primary endpoint of the phase 1 portion is to determine the MTD/RP2D of talimogene laherparepvec administered with neoadjuvant paclitaxel-doxorubicin/cyclophosphamide chemotherapy, safety/toxicity of the combination.

Phase 2 design:
Simon's two-stage optimal design (Simon, 1989) will be used for sample size selection to test the null hypothesis that the true response rate is .30 vs. the alternative that the true response rate is 0.45. After testing the drug on 12 evaluable patients in the first stage, the trial will be terminated if 3 or fewer respond. If the trial goes on to the second stage, a total of 25 evaluable patients will be studied for a total of 37 evaluable patients. If the total number responding is less than or equal to 14, the drug is rejected. This design yields a type I error rate of .0990 and power of .70 when the true response rate is .3. The probability of early stopping is .49.

The primary endpoint of the phase 2 portion of the study is the pathologic complete response rate (pCR, defined as absence of residual invasive carcinoma in the breast and ipsilateral draining lymph nodes) following the study treatment. This is to determine the efficacy of neoadjuvant talimogene laherparepvec in conjunction with neoadjuvant chemotherapy for early/locally advanced triple negative invasive breast cancer.
The analysis of the primary endpoint as a binomial variable (pathologic complete response vs. pathologic non-complete response) will be calculated along with its' 95% confidence intervals based on the exact binomial distribution.

10.2. **Sample Size/Accrual Rate**

Phase 1:
Between 9-12 patients will be accrued in the phase 1 portion of the study. The accrual rate is estimated at 1-2 patients per month.

Phase 2:

In the first stage, 12 patients will be accrued. If there are 3 or fewer pathologic complete responses in these 12 patients, the study will be stopped. Otherwise, 25 additional patients will be accrued for a total of 37 evaluable patients. Non-evaluable patients may be replaced to reach the accrual target of evaluable patients with sponsor and IRB approval. It is estimated that the center would accrue 1-2 patients per month for a total of 18 months. We anticipate that some of those patients may be unevaluable, and we estimate that accrual should be completed in 24 months.

10.3. Analysis of Secondary Endpoints

Secondary endpoints include; 5 year recurrence free survival/overall survival, immune activation correlatives by IHC and T cell receptor sequencing. Additional blood sampling for biomarker analysis.

10.4 Reporting and Exclusions

10.4.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment with talimogene laherparepvec.

10.4.2 **Evaluation of response.** All patients who have completed neoadjuvant chemotherapy and received at least three injections of talimogene (except in the case where the injections were stopped prior to the third injection due to resolution of the primary tumor on ultrasound) would be evaluable for the primary response endpoint. Patients should be categorized as pathologic 1) complete responder, 2) partial responders (any objective reduction in tumor burden with residual disease), 3) stable disease (no change), or 4) disease progression (any objective increase in primary lesion or development of new lesions on therapy). Patients who are not evaluable may be replaced with approval by the PI.

10.5 Data analysis plan

The pCR will be calculated along with its 95% confidence intervals based on the exact binomial distribution. Toxicity will be reported by type, frequency and severity. Survival probabilities for the time-to-event data will be estimated using the Kaplan Meier method with standard errors using Greenwoods formula. Other secondary endpoints will be summarized using descriptive statistics, and correlative analysis will be conducted using appropriate statistical methods.

11. CORRELATIVE EXPERIMENTS:

11.1. Immunohistochemistry analysis of breast tumor tissue:

Background: Analysis of tumor tissues using immunohistochemistry have identified immune factors associated with clinical benefit from systemic therapy. The immunoscore is a method to quantify the level of CD8+ and CD45RO+ T cells in tumor tissue. This system has shown promise in the prognostic evaluation of tumors such as colon cancer. The current correlative experiment will attempt to correlate the level of CD8+ and CD45RO+ infiltrates with pathologic complete response. In addition, staining of the post treatment resection specimen

for HSV viral proteins will be done to assess the level of viral replication at the tumor site and any available lymph nodes with grossly positive disease. These correlative studies will be performed on tissue samples from the diagnostic biopsy tissue collected from on treatment during a week 6 biopsy and grossly positive lymph nodes and resected breast tissue. Methods: The staining of the specimens will be adapted from the method used in Pages et al. JCO 2009 for the CD8+ and CD45RO+ infiltrate in the diagnostic core biopsy sample, a tissue sample from an on treatment core biopsy and the post treatment resected tumor area. Patient tissue staining will be carried out in our tissue core using a Vectra automated immunostainer after antibody optimization has been completed on appropriate controls. An image analysis will be carried out using our HALO digital pathology analysis software algorithms to provide a score of positive staining events/area of viable tumor analyzed. The score between those with pathologic complete response and those without will be compared on the core biopsy and resected tumor. This analysis will require one-two, 4 micron slides and one H&E slide from each specimen (pre-treatment core biopsy, on treatment core biopsy and post treatment resected specimen with the region surrounding the injection site selected for sectioning).

11.2 **T cell repertoire analysis of tumor specimens:** Background: Changes in the T cell repertoire occur during expansion of activated T cell clones to an antigenic stimulus (Speiser et al. J of Immunology 2006). Evaluation of the clonal diversity by sequencing the hypervariable CDR3 region of the T cell receptor can show if one or more immunodominant T cell clones emerge following treatment with talimogene laherparepvec. Characterization of this shift in tumor infiltrating lymphocytes during treatment may provide useful information on the clinical benefit from talimogene laherparepvec injection into the primary tumor site. In addition, RNAseq on the whole exome will be performed to obtain transcriptomics on these same samples to identify changes in gene transcription from baseline on therapy along with mutations that can be used as additional potential immunologic pharmacodynamic and predictive biomarkers to therapy with talimogene laherparepvec.

Methods: Five slides (5 microns each) from the diagnostic core biopsy and five slides from the resected tumor area and grossly positive lymph nodes will be sent for T cell receptor rearrangement sequencing to Adaptive Biotechnologies, 1551 EastLake Ave E, Suite 200 Seattle WA 98102. The RNAseq will be performed in the Moffitt Molecular Genomics Core using an Illumina Truseq whole exome assay optimized for RNA extracted from FFPE sections from these same tissue specimens (approximately 1 microgram of RNA input is required). One microgram of RNA will be collected from each specimen for each timepoint available. Gene expression analysis and mutation calls will be performed by Moffitt bioinformatics staff to analyze correlations with genomic data and clinicopathologic factors.

11.3 Flow cytometry biomarker Sampling
Background: Treatment of tumors with TVEC can lead to changes in tumor chemokines and host immune activation. While we are analyzing these changes in the tumor microenvironment it is desirable to evaluate circulating PBMCs and plasma samples for changes in PBMC populations and circulating chemokines during the study treatment.

Methods: Three sodium heparin tubes and one plasma separator tube will be collected at baseline, pre-dose on weeks 2, 5 and 9. This blood will be processed (PBMCs will undergo Ficoll separation, 1mL of plasma will be separated into 250 microliter aliquots) in Dr. Czerniecki's lab and stored in liquid nitrogen for batched analysis. Multiparameter flow cytometry will be performed on PBMCs for T cell subsets and functional activation. Cytometric bead assays will be performed on plasma aliquots for Th1/Th2 and chemokines.

11.4 Analysis of response on breast ultrasound and MRI:

Background: As part of their routine care, a number of patients in the trial underwent breast ultrasounds and MRI before and after TVEC+NAC treatment prior to surgery. These can be analyzed to evaluate treatment response on this additional imaging modality. An objective marker based on non-invasive multiparametric MRI (mpMRI) that can predict degree and spatial extent of tumor response to pre-operative TVEC+NAC could allow individual tailoring of neoadjuvant therapy and improved surgical margins in the future. Imaging biomarkers predictive of pCR can also aid in prognostic evaluation.
Methods: Retrospective review of the medical records of patients enrolled in the trial will determine which patients have pre and post-treatment, presurgical breast ultrasounds and MRIs for analysis. Reports and images will then be analyzed to evaluate treatment response. Report and image analysis will involve qualitative and quantitative analysis. Quantitative analysis of images will involve multispectral cluster analysis of tumor habitats that is well developed in the IRAT (Image Response Assessment Team) Core at MCC and has been applied to analyze patients in the MCC# 18596 trial (evaluating breast tumor response to pre-operative radiation treatment) to date. The MRI analysis involves pre-processing mpMRI to match voxel dimensions across patients, scans, and scan dates, then co-registering pre- and post-TVEC MRI images per patient to compute DCE-MRI parameter maps, compute ADC maps, and calibrate T2W intensities using reference normal tissues. The primary approach involves analysis of tumor voxels using Self-Organizing Maps (SOM), a technique that was developed through the IRAT Core. These microhabitat quantitative analysis techniques will also be compared to standard quantitative analysis of tumor volume response (eg. volume calculated from three orthogonal dimension measurements noted in the reports). MRI results will be compared to pathology reports to determine correlations. For ultrasound images changes in tumor size measurements at multiple timepoints from baseline will be analyzed to determine early predictors for complete pathologic response.

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APPENDIX A

Performance Status Criteria

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.

APPENDIX B TALIMOGENE LAHERPAREPVEC PI

1 INDICATIONS AND USAGE

IMLYGIC is a genetically modified oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.

Limitations of use: IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases.

2 DOSAGE AND ADMINISTRATION

For intralesional injection only. Do not administer intravenously.

2.1 Dose

Administer IMLYGIC by injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance.

IMLYGIC is provided in single-use vials of 1 mL each in two different dose strengths:

- 10^6 (1 million) plaque-forming units (PFU) per mL (light green cap) – for initial dose only
- 10^8 (100 million) PFU per mL (royal blue cap) – for all subsequent doses

Recommended Dose and Schedule

The total injection volume for each treatment visit should not exceed 4 mL for all injected lesions combined. It may not be possible to inject all lesions at each treatment visit or over the full course of treatment. Previously injected and/or uninjected lesion(s) may be injected at subsequent treatment visits. The initial recommended dose is up to 4 mL of IMLYGIC at a concentration of 106 (1 million) PFU per mL. The recommended dose for subsequent administrations is up to 4 mL of IMLYGIC at a concentration of 108 (100 million) PFU per mL. The recommended dosing schedule for IMLYGIC is shown in Table 1.

Table 1. Recommended Dose and Schedule for IMLYGIC

Treatment	Treatment Interval	Maximum Injection Volume per Treatment Visit (all lesions combined)	Dose Strength	Prioritization of Lesions to be Injected
Initial	–	4 mL	10^6 (1 million) PFU per mL	Inject largest lesion(s) first. Prioritize injection of remaining lesion(s) based on lesion size until maximum injection volume is reached or until all injectable lesion(s) have been treated.
Second	3 weeks after initial treatment	4 mL	10^8 (100 million) PFU per mL	Inject any new lesion(s) (lesions that have developed since initial treatment) first. Prioritize injection of remaining lesion(s) based on lesion size until maximum injection volume is reached or until all injectable lesion(s) have been treated.
All subsequent treatments (including reinitiation)	2 weeks after previous treatment	4 mL	10^8 (100 million) PFU per mL	Inject any new lesion(s) (lesions that have developed since previous treatment) first. Prioritize injection of remaining lesion(s) based on lesion size until maximum injection volume is reached or until all injectable lesion(s) have been treated.

Dose Volume Determination (per Lesion)

Use Table 2 to determine the volume of IMLYGIC injection for each lesion.

Table 2. Determination of IMLYGIC Injection Volume Based on Lesion Size

Lesion Size (longest dimension)	Injection Volume
> 5 cm	up to 4 mL
> 2.5 cm to 5 cm	up to 2 mL
> 1.5 cm to 2.5 cm	up to 1 mL
> 0.5 cm to 1.5 cm	up to 0.5 mL
≤ 0.5 cm	up to 0.1 mL

When lesions are clustered together, inject them as a single lesion according to Table 2.

Continue IMLYGIC treatment for at least 6 months unless other treatment is required or until there are no injectable lesions to treat. Reinitiate IMLYGIC treatment if new unresectable cutaneous, subcutaneous, or nodal lesions appear after a complete response.

2.2 Preparation and Handling

Healthcare providers who are immunocompromised or pregnant should not prepare or administer IMLYGIC and should not come into direct contact with the IMLYGIC injection sites, dressings, or body fluids of treated patients *[see Warnings and Precautions (5.1)]*.

Avoid accidental exposure to IMLYGIC and follow universal biohazard precautions for preparation, administration, and handling of IMLYGIC:

- Wear personal protective equipment (protective gown or laboratory coat, safety glasses or face shield, and gloves) while preparing or administering IMLYGIC.
- Avoid accidental exposure to IMLYGIC, especially contact with skin, eyes, and mucous membranes.
  - Cover any exposed wounds before handling.
  - In the event of an accidental occupational exposure (e.g., through a splash to the eyes or mucous membranes), flush with clean water for at least 15 minutes.
  - In the event of exposure to broken skin or needle stick, clean the affected area thoroughly with soap and water and/or a disinfectant.
- Treat all IMLYGIC spills with a virucidal agent such as 1% sodium hypochlorite and blot using absorbent materials.
- Dispose of all materials that may have come in contact with IMLYGIC (e.g., vial, syringe, needle, cotton gauze, gloves, masks, or dressings) in accordance with universal biohazard precautions.
- Advise patients to place used dressings and cleaning materials into a sealed plastic bag and dispose in household waste.

Thawing IMLYGIC Vials

1. Determine the total volume required for injection, up to 4 ml *[see Dosage and Administration (2.1)]*.
2. Thaw frozen IMLYGIC vials at room temperature [20º to 25ºC (68º to 77ºF)] until IMLYGIC is liquid (approximately 30 minutes). Do not expose the vial to higher temperatures. Keep the vial in original carton during thawing.
3. Swirl gently. Do NOT shake.
4. After thawing, administer IMLYGIC immediately or store in its original vial and carton, protected from light in a refrigerator [2° to 8°C (36° to 46°F)] for no longer than the specified duration in Table 3. Do not refreeze IMLYGIC after thawing. Discard any IMLYGIC vial left in the refrigerator longer than the specified times in Table 3.

Table 3. Storage Times for Thawed IMLYGIC Vial at 2° to 8°C (36° to 46°F)

10^6 (1million) PFU per mL	10^8 (100million) PFU per mL
12 hours	48 hours

5. Prepare sterile syringes and needles. A detachable needle of 18–26G may be used for IMLYGIC withdrawal and a detachable needle of 22–26G may be used for injection. Small unit syringes (e.g., 0.5 mL insulin syringes) are recommended for better injection control.
6. Using aseptic technique, remove the vial cap and withdraw the product from the vial into the syringe(s), noting the total volume. Avoid generating aerosols when loading syringes with product, and use a biologic safety cabinet if available.

2.3 Administration

Follow the steps below to administer IMLYGIC to patients:

Pre-Injection

1. Clean the lesion and surrounding areas with an alcohol swab and let dry.
2. Treat the injection site with a topical or local anesthetic agent, if necessary. Do not inject anesthetic agent directly into the lesion. Inject anesthetic agent around the periphery of the lesion.

Injection

1. Inject IMLYGIC intralesionally into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance. Using a single insertion point, inject IMLYGIC along multiple tracks as far as the radial reach of the needle allows within the lesion to achieve even and complete dispersion. Multiple insertion points may be used if a lesion is larger than the radial reach of the needle.

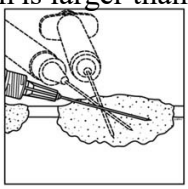

Figure 1: Injection administration for cutaneous lesions

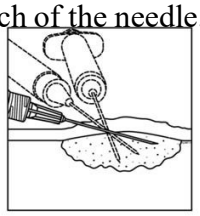

Figure 2: Injection administration for subcutaneous lesions

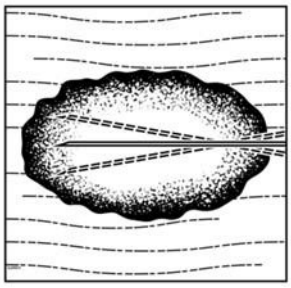

Figure 3: Injection administration for nodal lesions

2. Inject IMLYGIC evenly and completely within the lesion by pulling the needle back without exiting the lesion. Redirect the needle as many times as necessary while injecting the remainder of the dose of IMLYGIC. Continue until the full dose is evenly and completely dispersed.

3. When removing the needle, withdraw it from the lesion slowly to avoid leakage of IMLYGIC at the insertion point.

4. Repeat steps 1-2 under pre-injection and steps 1-3 under injection for other lesions to be injected.

5. Use a new needle any time the needle is completely removed from a lesion and each time a different lesion is injected.

Post-Injection

1. Apply pressure to the injection site(s) with sterile gauze for at least 30 seconds.

2. Swab the injection site(s) and surrounding area with alcohol.

3. Change gloves and cover the injected lesion(s) with an absorbent pad and dry occlusive dressing.

4. Wipe the exterior of occlusive dressing with alcohol.

5. Advise patients to:

- Keep the injection site(s) covered for at least the first week after each treatment visit or longer if the injection site is weeping or oozing.
- Replace the dressing if it falls off.

3. DOSAGE FORMS AND STRENGTHS

Initial dose only: 106 (1 million) PFU per mL solution in 1 mL single-use vial (light green cap)
Subsequent doses: 108 (100 million) PFU per mL solution in 1 mL single-use vial (royal blue cap)

4. CONTRAINDICATIONS

- **Immunocompromised Patients**

IMLYGIC is a live, attenuated herpes simplex virus and may cause life-threatening disseminated herpetic infection in patients who are immunocompromised. Do not administer IMLYGIC to immunocompromised patients, including those with a history of primary or acquired immunodeficient states, leukemia, lymphoma, AIDS or other clinical manifestations of infection with human immunodeficiency viruses, and those on immunosuppressive therapy *[see Nonclinical Toxicology (13.2)]*.

- **Pregnant Patients**

Do not administer IMLYGIC to pregnant patients.

5. WARNINGS AND PRECAUTIONS

- **Accidental Exposure to IMLYGIC**

Accidental exposure may lead to transmission of IMLYGIC and herpetic infection. Accidental needle stick and splashback to the eyes have been reported in healthcare providers during preparation and administration of IMLYGIC.
Healthcare providers, close contacts (household members, caregivers, sex partners, or persons sharing the same bed), pregnant women, and newborns should avoid direct contact with injected

lesions, dressings, or body fluids of treated patients [see Dosage and Administration (2.2)]. Healthcare providers who are immunocompromised or pregnant should not prepare or administer IMLYGIC.

Caregivers should wear protective gloves when assisting patients in applying or changing occlusive dressings and observe safety precautions for disposal of used dressings, gloves, and cleaning materials [see Dosage and Administration (2.2)].

In the event of an accidental exposure to IMLYGIC, exposed individuals should clean the affected area thoroughly with soap and water and/or a disinfectant. If signs or symptoms of herpetic infection develop, the exposed individuals should contact their healthcare provider for appropriate treatment [see Warnings and Precautions (5.2)].

Patients should avoid touching or scratching injection sites or their occlusive dressings, as doing so could lead to inadvertent transfer of IMLYGIC to other areas of the body.

- **Herpetic Infection**

In clinical studies, herpetic infections (including cold sores and herpetic keratitis) have been reported in patients treated with IMLYGIC. Disseminated herpetic infection may also occur in immunocompromised patients [see Contraindications (4.1)].

Patients who develop suspicious herpes-like lesions should follow standard hygienic practices to prevent viral transmission. Patients or close contacts with suspected herpetic infections should also contact their healthcare provider to evaluate the lesions. Suspected herpetic lesions should be reported to Amgen at
1-855-IMLYGIC (1-855-465-9442); patients or close contacts have the option of follow-up testing for further characterization of the infection.

IMLYGIC is sensitive to acyclovir. Acyclovir or other antiviral agents may interfere with the effectiveness of IMLYGIC. Therefore, consider the risks and benefits of IMLYGIC treatment before administering antiviral agents to manage herpetic infection.

- **Injection Site Complications**

Necrosis or ulceration of tumor tissue may occur during IMLYGIC treatment. Cellulitis and systemic bacterial infection have been reported in clinical studies. Careful wound care and infection precautions are recommended, particularly if tissue necrosis results in open wounds.

In clinical studies, impaired healing at the injection site has been reported. IMLYGIC may increase the risk of impaired healing in patients with underlying risk factors (e.g., previous radiation at the injection site or lesions in poorly vascularized areas). One patient had an amputation of a lower extremity 6 months after IMLYGIC injection due to an infected non-healing wound. This wound area had been treated with surgery and radiation prior to IMLYGIC treatment and had previous wound complications.

If there is persistent infection or delayed healing of the injection site(s), consider the risks and benefits of IMLYGIC before continuing treatment with IMLYGIC.

- **Immune-Mediated Events**

IMLYGIC may result in immune-mediated events. In clinical studies, immune-mediated events, including glomerulonephritis, vasculitis, pneumonitis, worsening psoriasis, and vitiligo have been reported in patients treated with IMLYGIC.

Consider the risks and benefits of IMLYGIC before initiating treatment in patients who have underlying autoimmune disease or before continuing treatment in patients who develop immune-mediated events.

- **Plasmacytoma at Injection Site**

In a clinical study, a plasmacytoma has been reported in proximity to the injection site after administration of IMLYGIC in a patient with smoldering multiple myeloma.

Consider the risks and benefits of IMLYGIC in patients with multiple myeloma or in whom plasmacytoma develops during treatment.

6. ADVERSE REACTIONS

The most commonly reported adverse drug reactions (≥ 25%) in IMLYGIC-treated patients were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain.

The following adverse reactions are discussed in greater detail in another section of the label:
Herpetic Infection [see Warnings and Precautions (5.2)]
Injection Site Complications [see Warnings and Precautions (5.3)]

- **Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of IMLYGIC was evaluated in 419 patients who received at least 1 dose of either IMLYGIC (n = 292) or subcutaneously administered granulocyte-macrophage colony-stimulating factor (GM-CSF) (n = 127) in an open-label, randomized clinical study of patients with stage IIIB, IIIC, and IV melanoma that was not considered to be surgically resectable *[see Clinical Studies (14)]*. The median duration of exposure to IMLYGIC was 23 weeks (5.3 months). Twenty-six patients were exposed to IMLYGIC for at least 1 year.

Most adverse reactions reported were mild or moderate in severity and generally resolved within 72 hours. The most common grade 3 or higher adverse reaction was cellulitis *[see Warnings and Precautions (5.3)]*.

Pyrexia, chills, and influenza-like illness can occur any time during IMLYGIC treatment but were more frequent during the first 3 months of treatment.
Table 4 below lists adverse reactions with a 5% or greater incidence in the IMLYGIC arm compared to the GM-CSF arm in the clinical study *[see Clinical Studies (14)]*.

Table 4. Adverse Reactions Reported with At Least a 5% Greater Incidence in Patients Treated with IMLYGIC Compared to GM-CSF

Adverse Reactions	IMLYGIC (n = 292)		GM-CSF (n = 127)	
	Any Grade n	Grade 3 n	Any Grade n (%)	Grade 3 n (%)
General disorders and administration site conditions				
Fatigue	147 (50.3)	6 (2.1)	46 (36.2)	1 (< 1)
Chills	142 (48.6)		11 (8.7)	
Pyrexia	125 (42.8)		11 (8.7)	
Influenza-like illness	89 (30.5)	2 (< 1)	19 (15.0)	
Injection site pain	81 (27.7)	2 (< 1)	8 (6.3)	
Gastrointestinal disorders				
Nausea	104 (35.6)	1 (< 1)	25 (19.7)	
Vomiting	62 (21.2)	5 (1.7)	12 (9.5)	
Diarrhea	55 (18.8)	1 (< 1)	14 (11.0)	
Constipation	34 (11.6)		8 (6.3)	1 (< 1)
Abdominal pain	26 (8.9)	2 (< 1)	3 (2.4)	
Musculoskeletal and connective tissue disorders				
Myalgia	51 (17.5)	1 (< 1)	7 (5.5)	
Arthralgia	50 (17.1)	2 (< 1)	11 (8.7)	
Pain in extremity	48 (16.4)	4 (1.4)	12 (9.5)	1 (< 1)
Nervous system disorders				
Headache	55 (18.8)	2 (< 1)	12 (9.5)	
Dizziness	28 (9.6)		4 (3.2)	
Respiratory, thoracic, and mediastinal disorders				
Oropharyngeal pain	17 (5.8)		1 (< 1)	
Investigations				
Weight decreased	17 (5.8)	1 (< 1)	1 (< 1)	

Other adverse reactions associated with IMLYGIC in the open-label, randomized study include glomerulonephritis, vitiligo, cellulitis, and oral herpes.

7. DRUG INTERACTIONS

IMLYGIC is sensitive to acyclovir. Acyclovir or other antiherpetic viral agents may interfere with the effectiveness of IMLYGIC. No drug interaction studies have been conducted with IMLYGIC.

8. USE IN SPECIFIC POPULATIONS

Pregnancy Risk Summary:
Adequate and well-controlled studies with IMLYGIC have not been conducted in pregnant women. No effects on embryo-fetal development have been observed in a study conducted in

pregnant mice. The design of the study limits application of the animal data to humans *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

If the patient becomes pregnant while taking IMLYGIC, the patient should be apprised of the potential hazards to the fetus and neonate. Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with IMLYGIC.

If a pregnant woman has an infection with wild-type Herpes Simplex Virus Type 1 (HSV-1) (primary or reactivation), there is potential for the virus to cross the placental barrier and also a risk of transmission during birth due to viral shedding. Infections with wild-type HSV-1 have been associated with serious adverse effects, including multi-organ failure and death, if a fetus or neonate contracts the wild-type herpes infection. While there are no clinical data to date on IMLYGIC infections in pregnant women, there could be a risk to the fetus or neonate if IMLYGIC were to act in the same manner.

Data

Animal Data

No effects on embryo-fetal development were observed when IMLYGIC was intravenously administered during organogenesis to immunocompetent pregnant mice at doses up to 4 x 108 (400 million) PFU per kg (60-fold higher, on a PFU per kg basis, compared to the maximum clinical dose). Levels of IMLYGIC DNA in pooled fetal blood were at or below the assay detection level. Study design limitations included: 1) administration of IMLYGIC expressing human granulocyte-macrophage colony-stimulating factor (huGM-CSF), which is not biologically active in mice; 2) unknown transplacental kinetics of IMLYGIC following intravenous administration in pregnant mice; and 3) unknown significance of IMLYGIC dose extrapolation from animal to human based on body weight.

- **Lactation**

Risk Summary

There is no information regarding the presence of IMLYGIC in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IMLYGIC and any potential adverse effects on the breastfed infant from IMLYGIC or from the underlying maternal condition.

ClinicalConsiderations

Because medicinal products can be found in human milk, a decision should be made whether to discontinue nursing or to discontinue IMLYGIC while nursing.

- **Females and Males of Reproductive Potential**

No nonclinical or clinical studies were performed to evaluate the effect of IMLYGIC on fertility.

- **Pediatric Use**

Safety and effectiveness of IMLYGIC have not been established in pediatric patients.

- **Geriatric Use**

In clinical studies, no overall differences in safety or efficacy were observed between geriatric patients (≥ 65 years old) and younger patients.

- **Renal Impairment**

No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of IMLYGIC.

- **Hepatic Impairment**

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of IMLYGIC.

10 OVERDOSAGE

There is no clinical experience with an overdose with IMLYGIC. Doses up to 4 mL at dose strength of 108 (100 million) PFU per mL every 2 weeks (maximum cumulative dose of 222.5 x 108 PFU) have been administered in clinical studies, with no evidence of dose-limiting toxicity. The maximum dose of IMLYGIC that can be safely administered has not been determined. In the event of a suspected overdose, the patient should be treated symptomatically and supportive measures instituted as required [see Warnings and Precautions (5)].

11 DESCRIPTION

IMLYGIC (talimogene laherparepvec) is a sterile suspension for intralesional injection. IMLYGIC is a live, attenuated HSV-1 that has been genetically modified to express huGM-CSF. The parental virus for IMLYGIC was a primary isolate, which was subsequently altered using recombinant methods to result in gene deletions and insertions.

Each vial contains 1 mL deliverable volume of IMLYGIC at either 1 x 106 (1 million) PFU per mL or 1 x 108 (100 million) PFU per mL concentrations and the following excipients: di-sodium hydrogen phosphate dihydrate (15.4 mg), sodium dihydrogen phosphate dihydrate (2.44 mg), sodium chloride (8.5 mg), myo-inositol (40 mg), sorbitol (20 mg), and water for injection.

The 106 (1 million) PFU per mL vial of IMLYGIC contains a clear to semi-translucent liquid following thaw from its frozen state. The 108 (100 million) PFU per mL vial of IMLYGIC contains a semi-translucent to opaque liquid following thaw from its frozen state. The liquid in each vial may contain white, visible, variously shaped, virus-containing particles.

Each vial of IMLYGIC may also contain residual components of VERO cells including DNA and protein and trace quantities of fetal bovine serum.

The product contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

IMLYGIC has been genetically modified to replicate within tumors and to produce the immune stimulatory protein GM-CSF. IMLYGIC causes lysis of tumors, followed by release of tumor-derived antigens, which together with virally derived GM-CSF may promote an antitumor immune response. However, the exact mechanism of action is unknown.

12.3 Pharmacokinetics

Biodistribution (withinthebody)andViralShedding(excretion/secretion) IMLYGIC viral DNA levels in various tissues and secretions were determined using a quantitative polymerase chain reaction (qPCR) assay. Infectious IMLYGIC at the injection sites and at some potential herpetic lesions was also quantified using viral infectivity assays.

Nonclinical data

Following repeat intratumoral administration in mice, IMLYGIC DNA was primarily detected in the tumor, blood, spleen, lymph node, liver, heart, and kidney. IMLYGIC DNA was not detected in bone marrow, eyes, lachrymal glands, nasal mucosa, or feces. The highest level of IMLYGIC DNA was found in the injected tumor. IMLYGIC DNA was found in the injected tumor through 84 days and in blood samples through 14 days after the last administration of IMLYGIC.

Clinical data

The biodistribution and shedding of intralesionally administered IMLYGIC are being investigated in an ongoing study measuring IMLYGIC DNA and virus in blood, oral mucosa, urine, injection site, and occlusive dressings. In the initial 20 patients with melanoma who received IMLYGIC intralesional injection at a dose and schedule similar to that of the clinical study *[see Clinical Studies (14)]*, available data indicate that IMLYGIC DNA was present in the blood in 17 (85%) patients and in urine of 4 (20%) patients during the study. The peak levels of IMYLGIC DNA in the urine were detected on the day of treatment. Infectious IMLYGIC virus was detected at the site of injection in 3 (15%) patients at a single time point each, and all within the first week after the initial injection. The exterior of the occlusive dressings was positive for IMLYGIC DNA in 14 (70%) patients during the study; however, no infectious virus was detected on the exterior of the occlusive dressing. The number of patients with measurable levels of IMLYGIC DNA on the exterior of occlusive dressings declined over time with no measurable DNA by the third treatment in 13 patients tested.

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

Repeated intratumoral administration at 2 x 108 (200 million) PFU per kg (30-fold maximum proposed clinical dose, extrapolated based on body weight) did not demonstrate any adverse effects in immunocompetent mice. Severe combined immunodeficient (SCID) mice administered repeat intratumoral injections of IMLYGIC at a dose of 30-fold maximum proposed clinical dose

developed systemic viral infection (viral inclusion bodies or necrosis in enteric neurons in the gastrointestinal tract, adrenal gland, skin, pancreatic islet cells, eye, pineal gland, and brain).

14 CLINICAL STUDIES

The safety and efficacy of intralesional injections of IMLYGIC compared with subcutaneously administered GM-CSF was evaluated in a multicenter, open-label, randomized clinical study in patients with stage IIIB, IIIC, and IV melanoma that was considered to be not surgically resectable. IMLYGIC was injected into cutaneous, subcutaneous, or nodal melanoma lesions and was not injected into visceral lesions. Previous systemic treatment for melanoma was allowed. Patients with active cerebral metastases, bony metastases, extensive visceral disease, primary ocular or mucosal melanoma, evidence of immunosuppression, or receiving treatment with a systemic antiherpetic agent were excluded from the study.

The study included 250 (57%) men and 186 (43%) women. The mean age was 63 (range: 22 to 94) years. Most patients (98%) were white. Seventy percent (70%) of patients had baseline Eastern Cooperative Oncology Group (ECOG) performance status of zero. Seventy percent (70%) of patients had stage IV disease (27% M1a; 21% M1b; and 22% M1c), and 30% had stage III disease. Fifty-three percent (53%) of patients had received prior therapy for melanoma (other than or in addition to surgery, adjuvant therapy, or radiation), and 58% were seropositive for wild-type HSV-1 at baseline.

A total of 436 patients were randomized to receive either IMLYGIC (n = 295) or GM-CSF (n = 141). IMLYGIC was administered by intralesional injection at an initial concentration of 106 (1 million) PFU per mL on Day 1, followed by a concentration of 108 (100 million) PFU per mL on Day 21 and every 2 weeks thereafter, at a dose of up to 4 mL per visit. GM-CSF was administered subcutaneously in 28-day cycles, i.e., 125 µg/m2 daily for 14 days followed by 14 days without GM-CSF administration.

Patients were to be treated for at least 6 months or until there were no injectable lesions. During this period, treatment could continue despite an increase in size in existing lesion(s) and/or development of new lesion(s), unless the patient developed intolerable toxicity or the investigator believed that it was in the best interest of the patient to stop treatment or to be given other therapy for melanoma. After 6 months of treatment, patients were to continue treatment until clinically relevant disease progression (i.e., disease progression associated with a decline in performance status and/or alternative therapy was required in the opinion of the investigator), up to 12 months. Patients experiencing a response at 12 months after the start of treatment could continue treatment for up to an additional 6 months, unless there were no remaining injectable lesions or disease progression. All patients were to be followed for survival status for at least 36 months.

The major efficacy outcome was durable response rate (DRR), defined as the percent of patients with complete response (CR) or partial response (PR) maintained continuously for a minimum of 6 months. Tumor responses were determined according to World Health Organization (WHO) response criteria modified to allow patients who developed new lesions

or disease progression of existing lesions to continue the treatment and be evaluated later for tumor response.

The DRR was 16.3% in the IMLYGIC arm and 2.1% in the GM-CSF arm in the overall study population. The unadjusted relative risk was 7.6 (95% CI: 2.4, 24.1), with a p-value < 0.0001. The median time to response was 4.1 (range: 1.2 to 16.7) months in the IMLYGIC arm.

There was no statistically significant difference in overall survival (OS) between the IMLYGIC and the GM-CSF arms. The median OS in the overall study population was 22.9 months in the IMLYGIC arm and 19.0 months in the GM-CSF arm (p = 0.116).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

- IMLYGIC is provided as a sterile frozen suspension in a single-use, cyclic olefin polymer (COP) plastic resin vial with a chlorobutyl elastomer stopper, aluminum seal, and polypropylene cap. Each vial contains a retrievable minimal volume of 1 mL.
- The vial cap is color coded:
  - 10^6 (1 million) PFU per mL is light green (NDC 55513-078-01).
  - 10^8 (100 million) PFU per mL is royal blue (NDC 55513-079-01).

Storage and Handling

- Store and transport IMLYGIC at −90°C to −70°C (−130°F to −94°F).
- Protect IMLYGIC from light.
- Store IMLYGIC in the carton until use.
- Thaw IMLYGIC immediately prior to administration *[see Dosage and Administration (2.2)]*.
- Do not draw IMLYGIC into a syringe until immediately prior to administration *[see Dosage and Administration (2.2)]*.

17 PATIENT COUNSELING INFORMATION

Advise patients and/or close contacts to:

- **Read the FDA-approved patient labeling (Medication Guide).**
- Follow instructions below to prevent viral transmission *[see Warnings and Precautions (5.1)]*:
  - Avoid direct contact with injection sites, dressings, or body fluids of patients.
  - Wear gloves when changing dressing.
  - Avoid touching or scratching injection sites.
  - Keep injection sites covered for at least the first week after each treatment visit or longer if the injection site is weeping or oozing. Replace dressing if it falls off.

- Dispose of used dressings and cleaning materials in household waste in a sealed plastic bag.

- Female patients of childbearing potential should use an effective method of contraception to prevent pregnancy during treatment with IMLYGIC *[see Contraindications (4.2) and Use in Specific Populations (8.1)]*.
- Close contacts who are pregnant or immunocompromised should not change dressings or clean injection sites *[see Warnings and Precautions (5.1)]*.
- In case of accidental exposure to IMLYGIC, clean the exposed area with soap and water and/or a disinfectant. Patients or close contacts with suspected herpetic infections should contact their healthcare provider to evaluate the lesions. Suspected herpetic lesions should be reported to Amgen at 1-855-IMLYGIC (1-855-465-9442); patients or close contacts have the option of follow-up testing for further characterization of the infection *[see Warnings and Precautions (5.1) and (5.2)]*.

AMGEN®

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Patent: http://pat.amgen.com/Imlygic/

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