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

NCT03921073

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CONSENT TO TAKE PART IN A CLINICAL RESEARCH STUDY AND AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

Study Title:	**A phase II study of talimogene laherparepvec (T-VEC) in the treatment of locally advanced cutaneous angiosarcoma**
Protocol Number:	**19878**
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INTRODUCTION

This consent and authorization form explains why this research study is being done and what your role will be if you choose to take part. You may choose not to take part in this study.

The goal of this clinical research study is to find if the investigational drug talimogene laherparepvec is effective in treating your condition of cutaneous angiosarcoma. Cutaneous Angiosarcoma is a rare malignant tumor showing blood or lymphatic vessel differentiation. Participants with this condition and, who failed other therapy in the past and who are willing to seek this alternative treatment, are being recruited in this study.

If you choose to take part in this research study you will be asked to sign and date this informed consent document. You will be asked to spend up to 52 weeks (approximately 12 months) in this study. You will also be followed every 6 months for 2 years by telephone, or in person to check your health condition. About 13 participants will take part in this study at Moffitt Cancer Center throughout the United States.

Participants will undergo screening procedures that involves routine examination, blood tests and imaging scans. After the screening visit is complete, if you qualify to continue in the study, you will undergo the study treatment visit. Treatment visits will involve study drug administration

and other clinic visits covered later in this document. After study treatment, you will have a few outpatient visits and follow-up which involves evaluating your health condition by routine clinic examination and procedures, later described in detail.

Your participation is voluntary, and you may stop your participation at any time. There will be no penalties or loss of benefits or opportunities if you do not participate or decide to stop once you start. Alternatives to participating in the study are later described in this document.

We do not know if you will receive any benefit from your participation. You will not be compensated for your participation.

You will be told about any new information found during the study that may affect whether you want to continue to take part.

Even if we publish the findings from this study, we will keep your study information private and confidential. Anyone with the authority to look at your records must keep them confidential.

If you are interested in learning more about this study, please continue reading the information below.

WHAT IS THIS STUDY ABOUT?

You are being asked to participate in a research study. The purpose of this study is to see if a product called talimogene laherparepvec would be helpful in the treatment of cutaneous angiosarcoma. Talimogene laherparepvec is a modified herpes simplex 1 virus that can destroy cancer cells while leaving normal cells alone. It would be injected directly into the tumor initially 3 weeks apart. Then the remaining injections will be given every 2 weeks directly into the primary tumor only, for up to one year of injections.

Talimogene laherparepvec (T-VEC) is currently FDA approved for cutaneous melanoma. Talimogene laherparepvec is called the “study drug” in this document. Talimogene laherparepvec is still experimental and has not been approved by any regulatory health agency (like the Food and Drug Administration [FDA] or European Medicines Agency [EMA]) for use in people with cutaneous angiosarcoma.

Talimogene laherparepvec is a modified form of herpes simplex virus (HSV) type-1 (the ‘cold sore’ virus). The virus’ genes were modified in a laboratory so that it produces a protein called human granulocyte macrophage colony-stimulating factor (GM-CSF) and multiplies and grows in tumor cells. Human GM-CSF is normally produced by various cells within the body and is used as a medicine to treat people with white blood cell counts that are too low. This modified herpes simplex virus type-1 is not designed to change any of your genes, but instead acts as an agent to act on tumor cells and stimulate your immune system. Talimogene laherparepvec is administered by injection with a needle directly into one or more tumors. Your study doctor will decide which tumors are injected. Talimogene laherparepvec is intended to work in two complementary ways: by directly destroying cells in the injected tumors, and by activating the body’s own immune cells to destroy the tumor cells throughout the body, not just in the area where it is injected.

This consent form gives you important information about this study to help you decide if you want to participate. It describes the purpose of this study, the study procedures, the possible risks, and provides information about your rights as a study participant.

Please take the time to read this information carefully. You should talk to the study doctor and his/her study staff about this study and ask any questions you have. You can also discuss this study with other people such as your family or personal doctor. If you decide to participate in this study, you will be asked to sign and date this form. You will receive a copy of the signed and dated form.

After you sign and date this form, the study doctor and his/her study staff will do some tests to see if you meet the study requirements. Your participation in this study is voluntary. You are free to say yes or no. If you do not want to participate, your regular medical care and legal rights will not be affected. Even if you join this study, you may stop at any time.

HOW DO I KNOW IF I CAN BE IN THIS STUDY?

Before you can start the study, the study doctor or study staff will talk to you about the study. Then you have to sign and date this form before the study doctor or study staff can begin the first part of the study called a screening period or baseline evaluation (to be performed within 1 week of Visit 1) to see if you qualify to be in the main part of the study. You will also have imaging testing by CT chest, abdomen, and pelvis with IV contrast to measure your tumor no more 4 weeks prior to Visit 1. Your study doctor will determine your eligibility to participate in the study.

WHAT WILL HAPPEN DURING THIS STUDY?

Your study participation is divided into Screening period, Study treatment period (visit at study doctor's office for T-VEC administration and other study procedures) and Follow-up/End of study treatment period.

Screening Period: Before you begin any part of this study, you must sign and date this consent form. You must be honest with your study doctor about your health history and medication use or it may not be safe for you to be in the study. If you decide to take part in the study, your study doctor must be sure that you are well enough to undergo the study treatment. This screening examination will involve:

- Imaging: CT chest, abdomen, and pelvis with IV contrast - to be performed within 4 weeks prior to initiation of study treatment
- Physical Exam including your height and weight
- Demographics and Medical History/Oncology History – including questions regarding tobacco and alcohol use
- Review of current medication list
- Vital Signs (blood pressure, heart rate, and temperature)
- Pregnancy Test - blood (only for females who are able to get pregnant)
- Anti-Herpes simplex virus antibody testing
- Blood tests to monitor your health
- Performance status evaluation (what type of daily activities you can do)
- A sample of your biopsy tissue will be used for this study. Punch biopsy will be performed during screening period
- Tumor measurement and cancer staging by imaging and ultrasound

- If you are eligible to participate in this study, you will undergo one or more of the study procedures described in this form at each study visit

Study Drug Administration:

On Week 1 study treatment period, during your study doctor visit, you will receive the talimogene laherparepvec injection into the tumor. If you decide to take part in this study, you will begin by having your tumor measured by calipers. While the virus is being prepared, you will have a physical exam done by your surgeon. The study doctor will then attach the syringe with the virus and begin to slowly inject the tumor with the virus across the longest portion of the tumor. After the entire dose of up to 4 cc of 10^6 plaque-forming units (PFU)/ml of T-VEC is injected into the tumor, the needle will be withdrawn. A clean occlusive dressing will be placed over the injection site. You will get instructions on how to care for the injection site. There will be a three week gap between the first virus injection and second one, then the virus injections are given once every 2 weeks (up to 4cc of 10^8 PFU/ml of T-VEC). If there is no tumor seen on ultrasound on a given injection day then no further talimogene laherparepvec will be injected.

Study Treatment Period (Week 1):

- Talimogene laherparepvec injection into the tumor, as described above
- Physical exam with tumor measurements
- Vital signs
- Weight
- Performance status
- Complete blood count
- Blood chemistry

Week 2 and Week 3 Study Doctor Visits:

- Review of current medication list
- Vital signs
- Weight
- Adverse Event Evaluation
- Tumor Measurement

Biweekly starting Week 4- Week 52

You will come to the study site for study drug T-VEC administration and other study procedures once every 2 week until Week 52. The following procedures will be performed:

- Talimogene laherparepvec injection into the tumor, as described above
- Physical exam with tumor measurements
- Review of current medication list
- Vital signs

- Weight
- Performance status
- Blood chemistry
- Complete blood count
- Adverse Event Evaluation

Week 5:

- Vital signs
- Weight
- Complete blood count

Week 6:

- Talimogene laherparepvec injection, into the tumor, as described above
- Physical exam with tumor measurements
- Vital signs
- Weight
- Performance status
- Blood chemistry
- Complete blood count
- Anti-herpes simplex virus antibody level (blood test)

End of Study Treatment:

- Physical exam
- Vital signs
- Weight
- Performance status
- Hematology
- Blood chemistry
- Tumor evaluation
- Immunohistochemistry testing
- Herpes simplex virus staining

Follow-up: Years 1-2

Telephone/chart follow up for recurrence and surveillance for any herpetic infections every 6 months.

WHILE YOU ARE IN THE STUDY, YOU MUST:

- Follow the instructions you are given.
- Come to the study center for all visits with the study doctor.
- Give correct and accurate information about your medical history and current medical condition.
- Tell the study doctor about any health problems you have during the study.
- Tell the study doctor about any new medicine or drug you take during the study.
- Not take any other drugs or remedies unless the study doctor has approved them beforehand. This includes prescription drugs and over the counter medicine (including vitamins and herbal remedies) that you buy without a prescription.
- Not participate in other medical research studies.
- Not get pregnant or cause your partner to become pregnant.
- Tell the study doctor or study staff if you want to stop being in the study at any time.

WHAT HAPPENS WHEN I COME FOR STUDY VISITS?

After you sign and date this form, the study doctor or study staff may do the things listed below when you come in for study visits. If you would like more information about which tests and procedures will be done at each study visit, ask the study doctor or study staff.

Medical History: The study doctor will ask you about past/present diseases and surgeries. The questions may also include any allergies, birth control procedures and medicines. Any other studies you were in may also be asked. Other questions may include any medical conditions or side effects which may occur during the study.

Vital Signs, Height and Weights: Check your blood pressure by putting a band around your arm (this will squeeze your arm for about a minute), check your pulse, listen to you breathe in and out, and take your temperature. Body weight is also recorded to see how much you weigh.

Demographic Data: At Screening, demographic information like your year of birth, gender, and ethnic origin will be collected if permitted by local regulations.

Physical examination: Including symptoms of your disease will be performed.

Concomitant Medication: You will be asked about the medications you take currently and the medications prohibited while on the study.

ECOG (Eastern Cooperative Oncology Group) Performance Status: This is a scale used by doctors to describe how well a patient is able to function. It assesses the patient's ability to do daily activities like bathing and getting around.

Tumor Biopsy/Core Needle Biopsy: These biopsies will be either core needle biopsies (or punch biopsies if skin lesions) depending on which type your study doctor thinks will be possible on your tumor.

Pregnancy Testing: You will have a blood pregnancy test (1 tsp or 5 milliliters) 72 hours prior to beginning the treatment on study. Women who are able to become pregnant must agree to use two effective birth control methods (for example: birth control pills, condoms) at the same time or practice complete abstinence from sexual contact with a man beginning 28 days before starting study treatment.

Tumor Measurement: Your tumor will be measured unless your disease shows progression and you are taken off study. The imaging is considered standard of care.

Computed tomography (CT) scan - is a type of X-ray scan. Several X-rays from different angles are sent through the body at one time. A computer processes the results to give a better picture than a standard, single X-ray scan. Also, a special dye is used to help improve the picture quality. The results are shown as a flat picture (length and width) displayed on a computer screen. Your chest, stomach area, and pelvic/hip area will be scanned. A small amount of dye is inserted into your vein just before the pictures are taken. CT scans will be performed at Screening and every 12 weeks.

MRI: An MRI machine or scanner uses a strong magnet and radio waves connected to a computer to create pictures of parts of the body. In this study, you will have an MRI of your of brain. The MRI unit is a large magnet that looks like a donut. A sliding table is in the opening. You will lie on the table and be comfortably positioned. In many cases, an extra piece of imaging equipment called a coil will be placed over the area of your body that is being imaged. The table will move into the opening. The technologist will be just outside the scanner room, but can see, hear, and speak to you at all times. During the exam, you will need to remain very still.

Blood samples: to check your blood cell counts, heart, liver, and kidney function and other standard safety tests during study treatment.

WHAT ELSE SHOULD I KNOW ABOUT THE STUDY PROCEDURES?

Your regular medical care might include some of the study tests and procedures. The study doctor or a member of the study staff can answer any questions you may have about which tests and procedures are not part of your regular medical care.

HOW WILL MY BIOPSY/BLOOD TISSUE SAMPLES BE USED?

In addition to the procedures outlined above, we are asking you to allow us to obtain and store samples of your tissue, and blood samples collectively referred to as “tissue” for use in future research. These samples may be used for research on your disease or condition and others to assist in the development of new treatments. We will use data collected during the study and biological samples obtained for research purposes to know the causes of cancer, its complications and other conditions for which individuals with cancer are at increased risk and to improve future treatment.

In addition to your sample being used for this study and future research, we would like to share it with other researchers, outside of the study. We will code your sample so that the researcher who uses it for other purposes does not know your identity. We will not release the code that links your sample to your personal identifying information for any reason.

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

Your sample will not be stored with your name or other identifying information and health information linked to it. We will not share your name or other information that identifies you unless it is required by law. During the conduct of the study, should you choose to withdraw

your consent to use the sample at a later date, please contact the study team. The study team will remove your sample from the research and immediately destroy it so that it can no longer be used. Please understand, withdrawal of consent with regard to biosample storage may not be possible after the study is completed. Please understand that part of your sample may have been used prior to the withdrawal of your consent.

CONSENT FOR OPTIONAL FUTURE USE OF SAMPLES

You are also being asked to allow the use of your samples for future research as described above.

You may decide not to allow the use of your samples for the optional future research. If you decide not to participate, your decision will have no impact on your ability to participate in the main study and will have no impact on any other benefits to which you would otherwise be entitled.

Please indicate your preference below:

❒**YES**_____(initials) I agree to allow the use of my samples for future research described above.

❒**NO**_____(initials) I do not agree to the use of my samples for future research described above.

ARE THERE RISKS TO ME IF I AM IN THIS STUDY?

Right now, we do not know for sure if talimogene laherparepvec will help. If it does not help, your condition/disease may get worse.

- You may have problems because of the study drug, talimogene laherparepvec, used in this study. These problems are called side effects. Some side effects are just bothersome. Others could harm you. There may be some side effects that we do not know about yet. The research might involve risks to you that are currently unforeseeable. Your study health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study drug. In some cases, side effects can be serious, long lasting, or may never go away.
- There are known side effects of this study on talimogene laherparepvec and its associated procedures.
- Talimogene laherparepvec may cause all, some, or none of the side effects listed below. There may also be unknown side effects from taking talimogene laherparepvec alone or with other drugs you may be taking. These side effects can be mild but could also be serious or even result in death. The majority of Amgen research studies with talimogene laherparepvec have been in people with malignant melanoma.

HERE ARE THE KNOWN SIDE EFFECTS THAT COULD HAPPEN WITH TALIMOGENE LAHERPAREPVEC

Very common side effects of talimogene laherparepvec (which may affect more than 1 person in 10):

- Flu-like illness: chills, fever, feeling tired, muscle pain, nausea and vomiting
- Injection site pain
- Headache
- Joint pain
- Arm or leg pain
- Diarrhea
- Constipation

Common side effects of talimogene laherparepvec (which may affect between 1 and 10 people in every 100):

- Injection site reactions: bleeding, redness, swelling, inflammation
- Skin infection caused by bacteria at the site of injection: symptoms may include fever, chills, redness or swelling at the injections site or site of the tumor, and may require hospitalization for antibiotic treatment.
- Wound complication at the injection site (secretion or discharge)
- Pain: pain after procedure, in the tumor, in the abdomen, throat pain, pain in the armpit or groin
- Abdominal discomfort
- Cold sore or fever blister in mouth (Oral herpes)
- Low red blood cell count (Anemia)
- Not feeling well (Malaise)
- Weight loss
- Dehydration
- Bruise
- Dizziness
- Skin or face becomes warm and reddened (Flushing)
- Rash
- Inflamed skin (Dermatitis)
- Blood clot (Deep vein thrombosis)
- Autoimmune reactions: Auto immune reactions to the body's own tissues have been reported in some patients administered with talimogene laherparepvec. Examples of autoimmune reactions that have been reported in patients receiving the study drug talimogene laherparepvec include:
    - inflammation of the kidneys (glomerulonephritis),
    - inflammation of the blood vessels (vasculitis),
    - inflammation of the lungs (pneumonitis),
    - areas of skin with loss of color (vitiligo),
    - if you already have psoriasis (itchy, flaky patches or scaling of the skin), it may get worse

  It is possible that an autoimmune reaction could occur in any part of the body. Please tell your study doctor if you have had any type of autoimmune disease before study

treatment with talimogene laherparepvec, and all treatments you are receiving for the disease.

Uncommon side effects of talimogene laherparepvec (which may affect between 1 and 10 in every 1000):

- Injection site reactions: warmth**,** injection site infection
- Eye infection caused by herpes virus (Herpetic keratitis)
- Difficulty breathing: People receiving talimogene laherparepvec have experienced difficulty breathing or the sensation of shortness of breath. In addition, if you have a tumor in your neck, your study doctor may warn you that you might experience compression of your airways during study treatment with talimogene laherparepvec. This might require a surgical procedure on the neck to open a direct airway. This occurred in a talimogene laherparepvec-treated patient who had a similar problem before treatment. A tube might need to be inserted into the opening in your throat. This tube may be connected to a machine to help you breathe.
- Plasmacytoma (a collection of abnormal antibody-producing white blood cells) may occur in the area where talimogene laherparepvec had been injected. Plasmacytoma may be associated with multiple myeloma (a cancer of white blood cells affecting the bone marrow).
- Symptoms of delayed wound healing at or around the injection site such as injection site discharge, foul odor, or dead tissue at the injection site. If you notice symptoms of delayed wound healing at the injection site(s), especially if you have risk factors such as diabetes, poor blood circulation, or have had radiation to the site, you should contact the study doctor or his/her study staff immediately.

Other potential side effects of talimogene laherparepvec

Arterial Hemorrhage

Some patients with a type of cancer in their neck area (called squamous cell cancer of the head and neck) who were treated with talimogene laherparepvec after suffering a recurrence of their cancer, following repeat surgery and radiation, experienced fatal bleeding from the main artery in their neck called the carotid artery. This occurred because the tumor was surrounding the carotid artery and when it was treated with the virus it caused blood to leak out rapidly from the neck. While this does not apply to cutaneous angiosarcoma participants in this study, we are informing all participants of this information so they are aware of all the safety information regarding talimogene laherparepvec.

Delay in response with talimogene laherparepvec study treatment

Given that talimogene laherparepvec may help by stimulating your immune system (immunotherapy), it is possible that there can be a delay in your body responding to the study treatment. In addition, you may also see an increase in the size of existing tumors and/or the development of new tumors before potentially seeing a response to talimogene laherparepvec.

Allergic reaction

As with any medication, you may have an allergic reaction to talimogene laherparepvec. Symptoms of an allergic reaction in general may include:

- Headache
- Rash
- Itching
- Flushing
- Swelling
- Shortness of breath
- Nausea
- Vomiting

Severe allergic reactions can cause dizziness, severe skin reactions, difficulty breathing or swallowing, a decrease in blood pressure, and could be life threatening. If you have symptoms of an allergic reaction, you should call 911 for immediate assistance. When it is safe to do so, contact the study doctor or his/her study staff to inform them of the reaction. If you have had an allergic reaction to talimogene laherparepvec or any of its ingredients, you should inform your study doctor.

Injection Site Reactions

Reactions at or near the area of the injection have been seen in other people administered talimogene laherparepvec. Symptoms include bleeding, redness, swelling and inflammation at the injection site. Skin infection caused by bacteria at the site of injection which may require hospitalization for antibiotic treatment have also been reported. Other symptoms may include warmth at the injection site or symptoms of delayed wound healing at or around the injection site such as injection site discharge, foul odor, or dead tissue at the injection site. If you notice symptoms of delayed wound healing at the injection site(s), you should contact the study doctor or his/her study staff immediately.

Side effects with Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF):

Talimogene laherparepvec contains genetic material that makes human GM-CSF. Human GM-CSF is a medicine used to treat patients with blood cell counts that are all low. Known side effects of human GM-CSF include, but are not limited to:

- Musculoskeletal pain
- Fever
- Chills
- Shortness of breath
- Rash
- Fatigue
- Gastrointestinal effects
- Fluid around heart and lungs.

Although the amount of human GM-CSF released when treating you with talimogene laherparepvec is very small, these side effects may still occur and your study doctor will be looking for them.

What are the risks of using talimogene laherparepvec in combination with other drugs?

Tell the study doctor or his/her study staff about any drugs you are taking, have recently taken or are planning to take, including drugs obtained without a prescription. These include drugs that are used to suppress the immune system, drugs that contain steroids (for example,

prednisone, cortisone), and drugs used to treat cancer. In addition, let your study doctor know if you are taking medicines, such as acyclovir, to treat or prevent herpes.

The side effects of using talimogene laherparepvec in combination with other drugs are unknown at this time. No formal drug interactions studies have been conducted with talimogene laherparepvec. Please discuss any concerns you may have with the study doctor.

Can talimogene laherparepvec be spread to my family members or other close contacts and how long after study treatment is this possible?

There have been no reported cases of spreading of talimogene laherparepvec to close contacts or family members in clinical trials or during regular treatment to date. However talimogene laherparepvec could potentially be spread to your family members or other close contacts (household members, caregivers, sex partners, or someone you share a bed with) at any time after your tumor(s) is/are injected with the study drug.

This may occur if your family member or other close contact touches the injection site or has contact with your body fluids or with the inside of the dressing(s) covering your injection site(s). Spreading talimogene laherparepvec may be more likely if your close contact has a break in the skin or mucous membranes that comes into contact with your injection site or your body fluids. Your study doctor will give you instructions on proper precautions to take after your injections.

In participants treated with talimogene laherparepvec in clinical trials, talimogene laherparepvec has been found on the surface of the injected tumors, up to 2 weeks after the injection, but not on the outside of the dressings that covered these injection sites. Small amounts of talimogene laherparepvec have been detected in participants' blood and urine for up to 1 week after injection. A study is ongoing to determine if talimogene laherparepvec can be detected in mucous membranes of the mouth and genitals.

Is there any risk to my family members or other close contacts if they are exposed to talimogene laherparepvec?

If a close contact has been exposed to talimogene laherparepvec, it is possible that they could develop symptoms of a herpes type infection. However, the chance of this happening is low due to the changes in talimogene laherparepvec that make it different from the naturally occurring herpes simplex virus, but you should know how to recognize these symptoms.

Most adults in the general population have been exposed to the naturally occurring herpes simplex (also known as "cold sore") virus (HSV-1). Common signs and symptoms of the naturally occurring herpes simplex virus include:

- Sores around the mouth ("cold sore", "fever blister") or the genitals ("genital sore").
- Blisters may develop on the fingers, ears or face.
- Infection of the cornea of the eye (keratitis) with eye pain, light sensitivity, discharge from the eyes or blurry vision
- Abdominal pain and infections, and inflammation inside the abdomen (infrequently).
- Rarely, serious infections of the brain (encephalitis) or spinal cord, causing paralysis (unable to move) have been reported. Signs may include fever, confusion or other behavior changes, headache, numbness and pain in the legs, constipation, or difficulty with urination.
- Life-threatening infections (disseminated herpes) can develop in people with a weakened immune system.

After infection, the naturally occurring herpes virus may travel to spinal nerve roots. The virus can reactivate from the nerve roots and cause recurrent cold sores or other signs of infection as described above. Stress, menstruation, and/or other illnesses are common triggers for reactivation of the naturally occurring virus.

Signs and symptoms of infection with talimogene laherparepvec could be similar to those described above, although talimogene laherparepvec has been changed to significantly reduce the chance of this happening.

What to do if you or a close contact develops any of the above symptoms:

- You should report any signs or symptoms to your study doctor right away. You should ask your close contact to call their doctor for evaluation and appropriate treatment.
- You or your close contact may be asked to come to the clinic for a test that may be able to determine if these symptoms may be due to talimogene laherparepvec.
- This test is likely to be most reliable if it can be performed in the first 3 days after symptoms develop.

Who should not have contact with talimogene laherparepvec?

Newborns and persons with severely weakened immune systems (such as those with acquired immunodeficiency syndrome (AIDS) or on chronic immune suppression drugs) should not be treated with talimogene laherparepvec as they may be at increased risk for serious, life-threatening herpetic infections after receiving talimogene laherparepvec. Tell your study doctor if you have a weakened immune system.

If your close contact or family member is pregnant or has a severely weakened immune system, they should not change your dressings or clean your injection sites. Keep used dressings and cleaning materials away from pregnant women, newborns, and those with weakened immune systems.

Are there any precautions I should take to prevent spread of talimogene laherparepvec to others?

- Avoid touching or scratching the injection site.
- Injection sites should be covered for 7 days after the injection with watertight dressings. If the dressing comes loose or falls off prior to 7 days after the injection, it should be replaced right away with a clean dressing. However, you may need to keep the dressing on longer if the lesions at the injection sites are weeping or oozing.
- Place all used dressings and cleaning materials in a sealed plastic bag, and throw them away as household waste or return to the study site for disposal as you are instructed by the study site staff.
- You should always observe proper hygiene. Wash your hands with warm water and soap after touching your injected lesions or handling the dressings to avoid potentially spreading talimogene laherparepvec to other persons.
- If you participate in this study, your study doctor and/or his/her study staff will provide you with additional instructions for injection site care.

What should I tell my close contacts while I am being treated with talimogene laherparepvec?

You should tell your close contacts to:

- Avoid direct contact with your injection sites and body fluids.

- Wear gloves while changing your dressings that cover your injected sites.

If your close contacts are accidentally exposed to talimogene laherparepvec, they should clean the affected area on their body with soap and water and /or a disinfectant. If they develop signs or symptoms of herpes infection, ask them to call their doctor, and you should report this to your study doctor.

Can talimogene laherparepvec be transmitted through sexual contact?

The naturally occurring herpes simplex virus (HSV-1) can be transmitted through sexual contact. It is not known if talimogene laherparepvec will behave the same way, thus you or your partner should use a latex condom during study treatment and for up to 30 days after your last dose when engaging in sexual activity to prevent possible transmission of talimogene laherparepvec. For those with latex allergies, polyurethane condoms may be used.

Is there any risk to your unborn children if you take part in this study?

It is not known if talimogene laherparepvec is harmful to an unborn or breastfed baby.

If you become pregnant during this study, potential risks could include complications such as a miscarriage (loss of the pregnancy) or birth defects.

Also, there is the possibility that a pregnant woman with a naturally occurring genital herpes infection could pass the infection to her baby. If this occurs, a herpes infection in an infant can cause serious effects, including damage to the baby's eyes, brain, and other internal organs, and may be fatal.

There is no evidence to date that such complications would occur with talimogene laherparepvec. However, if talimogene laherparepvec were to act in the same manner as the naturally occurring herpes simplex virus, it is possible that it could have the same effects on the baby if used during pregnancy.

It is not known if talimogene laherparepvec is transferred into breast milk.

If you are breastfeeding and wish to be in this study, you will be required to discontinue nursing during study treatment with talimogene laherparepvec plus chemotherapy and for an additional 3 months after the end of study treatment with talimogene laherparepvec plus chemotherapy. You should not resume breastfeeding until this has been discussed and approved by your study doctor.

Females

Pregnant or breastfeeding women, and women planning to become pregnant or planning to breastfeed, should not participate in this study. If you could become pregnant (that is, you are not postmenopausal or have not had surgery to remove your uterus, both ovaries or both fallopian tubes), you should let your sexual partner know you are in this study and you should use acceptable method(s) of effective birth control while you are receiving talimogene laherparepvec and for an additional 3 months after the last dose of talimogene laherparepvec.

Males

If your female partner could become pregnant you should let her know you are in this study and use appropriate birth control as described below during the study and for 30 days following your last dose of study drug.

Acceptable method(s) of effective birth control

You and the study doctor should discuss and agree on how you will prevent pregnancy.

If you plan to have vaginal sex during this study, you should understand that even with the use of acceptable method(s) of effective birth control, there is still a small chance that a pregnancy could occur. Acceptable method(s) of effective forms of preventing pregnancy include:

- Not having sex (abstinence)
- Surgical contraceptive methods:
- Vasectomy - Male participants who have had a vasectomy (surgery to become sterile and testing shows there is no sperm in the semen) or female participants whose male sexual partner has had a vasectomy.
- Surgery to tie both fallopian tubes. Female participants who have had both fallopian tubes tied or male participants whose female sexual partner has had both fallopian tubes tied.

You may also select one of the following birth control options:

Use of hormonal birth control methods: pills, shots/injections, implants (placed under the skin by a health care provider), or patches (placed on the skin)

Intrauterine devices (IUDs)

Two barrier methods (each partner must use one barrier method) with a spermicide.

Males must use a male condom (latex or other synthetic material) with spermicide.

Females must choose either a diaphragm with spermicide, cervical cap with spermicide, or contraceptive sponge (spermicide is already in the contraceptive sponge).

Note: Barrier methods have a higher failure rate than the other methods listed. To be considered acceptable, each partner must use one method with a spermicide. A female and male condom cannot be used together due to the risk of one the condoms tearing.

What if you or your partner becomes pregnant during the study?

Females

If you become pregnant, think you are pregnant or breastfeed during this study or within 3 months after stopping talimogene laherparepvec, please tell the study doctor or his/her study staff right away. The use of talimogene laherparepvec may be stopped. The study doctor will notify Amgen of the pregnancy, or that you are breastfeeding and discuss any follow-up with you. You will be asked to provide information on the pregnancy or breastfeeding outcome.

There is a risk of transmitting herpes virus to the baby when passing through the birth canal of a mother with a genital herpes infection. You should tell your study doctor if you have had a genital herpes infection or think you may have one while on this study. Your study doctor may recommend a Caesarean Section if you have signs of a genital herpes infection around the time you will give birth.

Males

If your partner is pregnant when you begin this study or becomes pregnant during this study, you must tell the study doctor or his/her study staff right away. The study doctor will notify Amgen of the pregnancy, discuss any follow-up with you (and/or your pregnant partner), and

ask you (and/or your pregnant partner) for information on the pregnancy outcome. Your partner will be asked to sign a separate consent before any information on her pregnancy can be collected.

UNFORESEEN RISKS

Since the use of the study drug is investigational, there may be other risks that are unknown. Additionally, there may be unknown risks to a pregnancy, embryo, or fetus if you or your female partner become pregnant.

ALTERNATIVE TREATMENT:

You do not have to be in this study to receive treatment for your condition. Other treatments available for your condition include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study of an investigational drug
- Getting no treatment.

If you decide that you don't want any more active treatment, one of your options is called "comfort care", also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible. If you think you might prefer comfort care, please discuss this with your family, friends and your study doctor.

A more complete listing of side effects for other therapies may be available for you to review if you wish. Please talk with your study doctor about the benefits and risks of any alternative methods of treatment that are available.

WHAT CAN HAPPEN IF I GET INJECTIONS?

Injections may cause the following problems:

- irritation of the vein; your skin near the vein could become warm, swell, hurt, or get red
- damage to your vein
- damage to the skin or tissue around the injection site
- a blood clot or an air bubble could form, which could block a blood vessel in another part of your body

Some of these problems could be very serious. Over time, getting a lot of injections can cause a vein to become hard or scar, which can make it difficult to put a needle into the vein to give you a shot or take blood.

COULD I HAVE ANY OTHER PROBLEMS WITH MY HEALTH IF I DO THIS RESEARCH STUDY?

It is possible that you could have problems and side effects of talimogene Laherparepvec that nobody knows about yet, which include your condition getting worse or even death.

It is possible that taking talimogene laherparepvec with your regular medications or supplements may change how talimogene laherparepvec, your regular medications, or your regular supplements work. It is very important that you tell the study doctor about all medications or supplements you are taking during the study.

WHAT ARE THE RISKS OF STUDY PROCEDURES?

Blood drawing: Needle sticks carry some risks such as fainting, bleeding, bruising, discomfort, dizziness, infection and/or pain at the puncture site.

***Tumor biopsy*:** Risks include pain, discomfort, soreness, redness, swelling, bleeding, bruising, and/or drainage at the biopsy site, abnormal wound healing, fever, infection, allergic reaction to the medication used to numb the skin over the biopsy site, and missed abnormal tissue requiring the need for another biopsy.

A biopsy procedure will involve removing a part of your tumor. A core needle biopsy is a percutaneous ("through the skin") procedure that involves removing small samples of tumor tissue using a hollow "core" needle. An “excisional” biopsy is a surgical procedure where an entire mass or abnormal area is removed. In all procedures, the area around the tumor will be anesthetized with an injection to help ease the pain and a sample will be removed either by cutting it out or removing tissue through a hollow "core" needle. There may be some bruising, bleeding, and soreness. There is a risk of the biopsy site getting infected. You may also be given medicine to make you sleepy.

CT scans: There is a slight risk of developing an allergic reaction to the contrast material. Be sure to tell your study doctor if you have allergies of any kind, such as hay fever, iodine allergy, eczema, hives, or food allergies. There is always a slight risk from being exposed to any radiation, including the low levels of X-rays used for a CT scan. However, the risk from the X-rays is usually very low compared with the potential usefulness of the test to manage your study treatment.

NEW FINDINGS

If the study doctor learns any new information about talimogene laherparepvec that might change your mind about continuing in the study, the study doctor or study staff will tell you about it. The study doctor will also tell you if new treatments become available for your condition.

WILL BEING IN THIS STUDY HELP ME?

If you agree to take part in this study, there may or may not be direct medical benefit to you. Your condition may even get worse during the study. The information collected during this study will help the doctors and researchers to learn more about the study drug combination that may

benefit you and other people with melanoma. However, there is no guarantee that this will happen.

WHO IS PAYING FOR THIS STUDY?

Moffitt Cancer Center is the sponsor of the study. Talimogene laherparepvec, the study drug is manufactured by Amgen and will be provided by them to you at no cost.

WILL IT COST ANYTHING TO BE IN THIS STUDY?

You and/or your insurance company will be financially responsible for hospital inpatient, outpatient and follow-up visits that would normally or routinely occur in the management of your disease. Inpatient and outpatient visits could include charges for treatments, medications, physician visits, laboratory tests and procedures. You and /or your insurance company will be responsible for paying for the charges which are considered routine, since you would have received these services even if you were not participating in this study. You will be responsible for any costs not covered by your insurance company, including deductibles, co-payments and all out-of-pocket expenses. Before you agree to be in this study, you should contact your health insurer to see if your plan will cover the costs required as part of your participation.

You and/or your insurance company will not be responsible for paying for study related items and services that are specifically required for this research study and are not considered part of the routine management of your disease, if these procedures are performed at Moffitt Cancer Center.

During your participation in this study, Amgen will be responsible for providing the study drug, talimogene laherparepvec (T-VEC), at no additional charge to you. You and/or your insurance company will be responsible for the charges related to the administration of the study drugs.

If you would like more information on the costs of being on this study or have other insurance related questions then please let your clinical trial coordinator know or contact our Business Office at 813-745-8422.

WHAT IF I GET HURT OR SICK WHILE I AM IN THIS STUDY?

If you need emergency care:

- Call 911 or go to your nearest emergency room right away. Moffitt Cancer Center does not have an emergency room or the facilities to provide emergency care.

If you do NOT need emergency care:

- Call or go to your regular doctor. It is important that you tell your regular doctor that you are participating in a research study. If possible, take a copy of this consent form with you when you go.

If you experience a side effect or a change in the way that you feel, call the study doctor at the telephone number listed on the first page of this form.

By signing and dating this informed consent and research authorization form, you have not given up any legal rights to seek compensation for injuries from the sponsor**.**

MOFFITT CANCER CENTER INJURY STATEMENT

If you believe you have been injured as a result of your participation in this study or if you have questions about your rights as a person who is taking part in a research study, you may call the Moffitt Cancer Center Risk Manager at 813-745-7882. Moffitt Cancer Center and its investigators have made no provision for monetary compensation in the event of physical illness or injury resulting from this study. Likewise, Moffitt Cancer Center and its investigators have made no provision for payment of lost wages, disability, or discomfort in the event of physical illness or injury resulting from this study. Florida law (Statute 768.28) limits the liability of Moffitt Cancer Center. This statute provides that damages are available only to the extent that negligent conduct of a Moffitt Cancer Center employee caused your injuries, and are limited by law.

WILL I GET PAID?

You will not be paid for taking part in this research study. You have no rights to and will not receive payments of any kind for discoveries, patents or products that may be developed from this study.

DO I HAVE TO REMAIN ON THIS STUDY ONCE I JOIN?

Your participation in this study is voluntary and you do not have to participate. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

Tell the study doctor if you are thinking about stopping or deciding to stop. If you do decide to stop your participation in the study, your study doctor will tell you how to stop safely and will discuss with you what follow-up care or testing would be helpful to you. The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

ARE THERE REASONS THE STUDY DOCTOR OR SPONSOR MIGHT TAKE ME OUT OF THE STUDY LATER?

Even if you want to stay in the study, there may be reasons the study doctor or study staff will need to take you out of it. Your study doctor has the right to take you out of the study at any time with or without your agreement. Your participation may be ended without your consent for different reasons, including the following:

- If the study doctor believes, for any reason, that it is in your best interest.
- If at any time while you are taking the study drug the study doctor discovers that your disease has worsened.
- If you develop side effects that the study doctor considers unacceptable.
- If you refuse to take the study drug or return for follow-up as recommended by your study doctor, or do not follow the study doctor’s instructions.

- If you refuse to have tests that are needed to determine whether the study drug is safe and effective.
- If you require treatment with drugs that are not allowed on this study.
- If other causes prevent you from continuing in this study.
- If the Sponsor decides to end the study.

HOW WILL MY INFORMATION BE KEPT CONFIDENTIAL?

We understand that information about you and your health is personal, and we are committed to protecting the privacy of that information. Because of this commitment and because of federal law, we must obtain your written authorization before we use or disclose your information for this study.

By signing this form, you are permitting researchers at Moffitt Cancer Center to use personal health information for research purposes within its organized health care arrangements. You are also allowing the Moffitt Cancer Center to disclose your personal health information to outside organizations or individuals that participate in this study. We may publish what we find out from this study. If we do, we will not let anyone know your name. We will not publish anything that would directly let people know who you are.

Identifiers will be removed from your identifiable private information or identifiable biospecimens collected during this study and could then be used for future research studies or distributed to another investigator for future research studies without additional informed consent.

WHO WILL DISCLOSE, RECEIVE, AND/OR USE YOUR INFORMATION?

Your records are confidential and they will be kept in a secure environment and protected to the full extent of the law

To do this research, the following people and/or organization(s) will be allowed to disclose, use, and receive your information, but they may only use and disclose the information to the other parties on this list, to you or your personal representative, or as permitted by law:

- Every research site for this study, including the Moffitt Cancer Center, and each site's study team, research staff and medical staff.
- Any person who provides services or oversight responsibilities in connection with this study.
- Every member of the Moffitt Cancer Center workforce who provides services in connection with this study.
- The person who is responsible for the study nationwide or worldwide (study chairperson).
- Any laboratories, individuals, and organizations that use your health information in connection with this study.
- Any sponsor of the study, including the following sponsors: Moffitt Cancer Center and Amgen (supplying study drug).
- Any federal, state, or local governmental agency that regulates the study (such as the U.S. Food and Drug Administration (FDA) and Florida Department of Health (FDH), the U.S. Department of Health & Human Services (DHHS), Office for Human Research Protections (OHRP).
- Other government agencies in this or other countries.

- The designated Protocol Review and Monitoring Committees, Institutional Review Boards such as Advarra IRB, Privacy Boards, Data and Safety Monitoring Board and their related staff that have oversight responsibilities for this study.
- The National Cancer Institute in evaluating the ongoing research of the Moffitt Cancer Center as a Comprehensive Cancer Center.

The organizations and people listed above may employ or pay various consultants and companies to help them understand, analyze and conduct this study. All of these people may not be known now, but if you would like to have more specific information about this at any time during the study, you may ask the study doctor and your questions will be answered.

Moffitt Cancer Center cannot guarantee the privacy of your information, or block further use or distribution, after the information has left the Moffitt Cancer Center. Others listed above may further disclose your information, and it may no longer be covered by federal privacy regulations. If all information that does or can identify you is removed from your records, the remaining information will no longer be subject to this authorization and may be used or shared for other purposes. You might have the right to see and copy your health records related to this research. You might not be able to see or copy some of your records until after all participants finish the study. If it is necessary for your care, your records will be provided to you or your regular doctor.

WHAT INFORMATION WILL BE USED OR DISCLOSED?

By signing below, you authorize the use and disclosure of your entire study record and any medical or other records held by Moffitt Cancer Center, including, but not limited to, HIV/AIDS, mental health, substance abuse or genetic information. The purpose for the uses and disclosures you are authorizing is to conduct the study explained to you during the informed consent and research authorization process and to ensure that the information relating to that study is available to all parties who may need it for research purposes.

Your authorization to use your health information will never expire unless and until you expressly revoke it in writing to the study doctor listed on the first page of this form.

Any data collected before your letter will continue to be used as necessary to preserve the integrity of the study, however no additional information will be collected after you withdraw your authorization.

You will receive a signed and dated copy of this form.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact:

- By mail:
  Study Participant Adviser Advarra
  IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Participant Adviser: Pro00032870.

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's (NCI) Information Service at: 1-800-4-CANCER (1-800-422-6237).

Visit the NCI's Websites at:

- CancerTrials: comprehensive clinical trial information at: http://cancertrials.nci.nih.gov
- CancerNet: accurate cancer information including PDQ at: http://cancernet.nci.nih.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

STATEMENT OF CONSENT

I have read this form and its contents were explained to me. I agree to be in this research study for the purposes listed above. All of my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records.

_____

Printed Name of Participant

_____ _____

Signature of Participant Date

STATEMENT OF PERSON OBTAINING INFORMED CONSENT / RESEARCH AUTHORIZATION

I attest that the participant named above had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to be in this study.

_____

Printed Name of Person Explaining Consent

_____ _____

Signature of Person Explaining Consent Date