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TITLE: Neoadjuvant Intralesional Injection of Talimogene Laherparepvec with Concurrent Preoperative Radiation in Patients with Locally Advanced Soft Tissue Sarcomas

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Study Agent: Talimogene Laherparepvec
Other Agent(s): Standard external beam radiation

Investigational Agent	IND#	IND Sponsor
Talimogene Laherparepvec	16359	Mohammed Milhem

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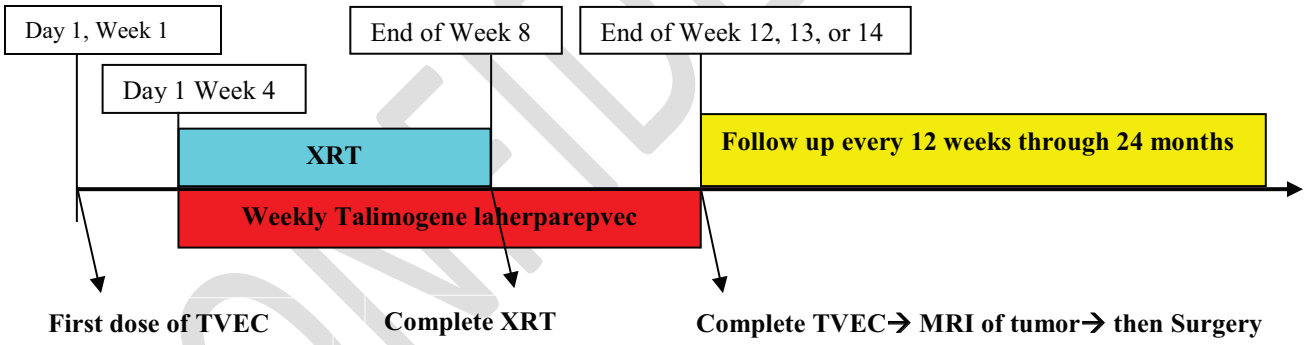
SCHEMA

Study Timeline Schema:



Phase 1b schema:

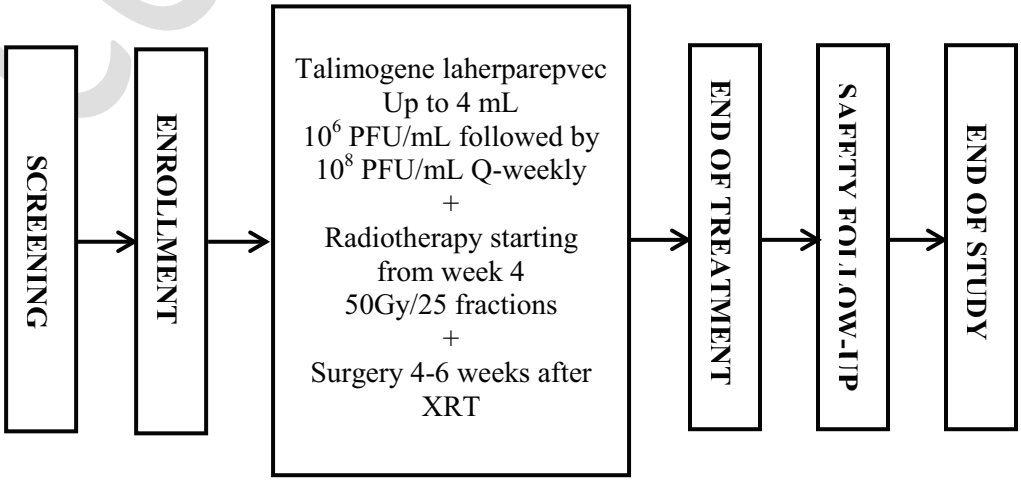


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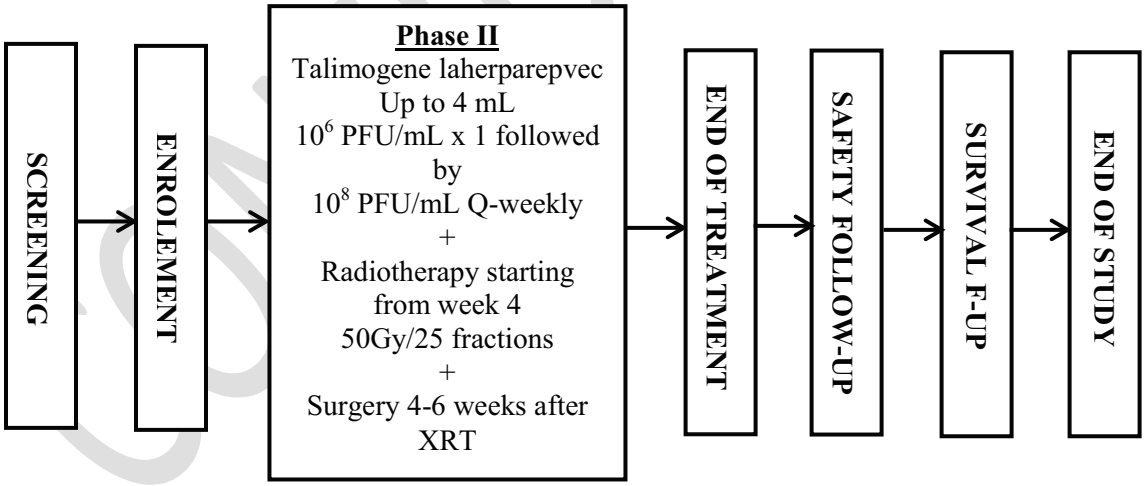
Table 1. Phase 1b Dose De-escalation Schedule

Number of Patients with DLT at a Given Talimogene Laherparepvec Dose	**Decision Rule**
≥ 2	Dose level will be declared toxic. If this is the lowest dose level, stop the study due to excessive toxicity; otherwise enter *three* additional patients at the next lowest dose level.
≤ 1 out of 3	Enter *three* more patients at this dose level.
≤ 1 out of 6	This is the recommended dose for the subsequent pilot study.

Talimogene Laherparepvec Dose Levels:
Dose 0 = talimogene laherparepvec up to 4.0 mL of 10^8 PFU/mL dosed weekly
Dose -1 = talimogene laherparepvec up to 4.0 mL of 10^8 PFU/mL dosed every 2 weeks.

- Initial dose for all = talimogene laherparepvec up to 4.0 mL of 10^6 PFU/mL

Phase 2 Schema:



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1. BACKGROUND

1.1 Disease Background

Adult soft tissue sarcomas (STS) constitute a wide heterogeneous group of very rare tumors, both in terms of histology and biological and clinical behavior. In contrast to major advances in the biological understanding of these heterogeneous subtypes, forward progress in the systemic treatment of sarcoma has been painstakingly slow. The prognosis of patients with metastatic or recurrent disease is poor and most of them will die from tumor progression. Taking into account differences in histology subtype, anatomic location of disease and age at disease onset, the overall median survival for patients with metastatic STS is approximately one year and only about 10% of these patients are alive at five years.[1]

Control of localized disease is, therefore, of prime importance as evidenced by the National Comprehensive Cancer Network's (NCCN) current treatment guidelines.[2] Pisters et al demonstrated that histologic grade, depth of location, and positive surgical margins are key determinants of STS recurrence.[3] However, patients typically present late with local tumor extensions into critical adjacent structures, making complete surgical resection with uninvolved margins difficult. Preoperative radiotherapy has been shown to significantly improve local disease control, functional outcomes and survival in patients with locally advanced STS.[4-6]

1.2 Talimogene Laherparepvec

Talimogene laherparepvec (HSV-1 [strain JS1]/ICP34.5-/ICP47-/hGM-CSF) is an oncolytic immunotherapy, formerly known as OncoVEX^{GM-CSF}, an immune-enhanced, oncolytic herpes simplex virus type 1 (HSV-1). Talimogene laherparepvec is a replication-competent HSV-1 designed for intratumoral injection. Talimogene laherparepvec was constructed using a new isolate of HSV-1 (strain JS1; ECACC Accession Number 01010209) and has been sequenced. The neurovirulence factor ICP34.5 and the ICP47-encoding genes are functionally deleted in the virus. The ICP34.5 functional deletion allows the virus to replicate selectively in tumors. The role of ICP47 is to block antigen presentation to major histocompatibility complex (MHC) class I and II molecules by blocking the transporter associated with antigen processing 1 and 2 (TAP1, TAP2). This deletion also allows the increased expression of the US11 gene. This promotes virus growth in cancer cells without decreasing tumor selectivity. The virus contains the coding sequence for human GM-CSF, a pleotrophic cytokine involved in the stimulation of cellular immune responses.

Development of talimogene laherparepvec was conducted in conjunction with the International Conference on Harmonization (ICH) guidance on oncolytic viruses. The therapeutic strategy for talimogene laherparepvec is to effect tumor cell death by lytic virus replication following direct intratumoral injection, combined with induction of an anti-tumor immune response enhanced by the local expression of GM-CSF. This combination of direct lysis of the injected tumor plus enhancement of the patient's own immune response is intended to result in both local and distant tumor destruction, and to prevent future progression of disease.

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The preparation and testing of the cell banks, viral seed stock, and talimogene laherparepvec clinical material were conducted in accordance with current Good Manufacturing Practices (cGMP), relevant ICH guidelines, European Directives, and the US Pharmacopeia and Title 21 Code of US Federal Regulations. In particular, the European Pharmacopoeia (Ph Eur) monograph on viral vaccine testing, ICH considerations on Oncolytic Viruses, and Food and Drug Administration (FDA) Points to Consider – Characterization of Cell Lines Used to Produce Biologicals (1993) have been followed for the safety testing of talimogene laherparepvec.

Talimogene laherparepvec has been studied in several clinical trials in multiple tumor types. A summary of talimogene laherparepvec's pertinent efficacy results and safety data follow. After intra-tumoral injection, talimogene laherparepvec is generally cleared from subjects' blood and urine within 48 hours. Rarely, extremely low levels of virus have been detected on the surface of injected tumors for up to 2 weeks following a single dose. 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. Subsequent studies have therefore used a lower initial dose (see below). No evidence of herpes infection attributable to talimogene laherparepvec has been documented in study subjects. While a number of individuals (subjects or medical personnel) have had reactivations of wild type HSV-1, which is not unexpected in the population as a whole, it was determined by culture of the virus and polymerase chain reaction (PCR) analysis not to be caused by talimogene laherparepvec.

Please refer to the talimogene laherparepvec Investigator Brochure (IB) for descriptions of all available data.

1.2.1 Talimogene Laherparepvec Clinical Experience

Nine clinical studies have been or are being conducted in several advanced tumor types including advanced solid tumors, melanoma, squamous cell cancer of the head and neck, and pancreatic cancer.[28]

These studies include a phase 1 study to evaluate the safety, bio-distribution, and biological activity of differing dose levels of talimogene laherparepvec in patients with advanced solid tumors.[27] In this open-label, ascending-dose study, single doses of talimogene laherparepvec either 10^6, 10^7, or 10^8 plaque forming units/mL (PFU/mL) (up to 4 mL), were injected directly into a single metastatic skin or subcutaneous tumor of breast cancer, head and neck cancer, gastrointestinal cancer, or melanoma. This study, as reported by Hu et al, identified that subjects who are seronegative for HSV-1 more commonly developed febrile flu-like symptoms and erythematous skin rashes at higher initial doses of talimogene laherparepvec (10^7 and 10^8 PFU/mL) compared to a decreased initial dose of 10^6 PFU/mL.[27]

In a phase I/II upward-titration study to assess the safety and biological activity of three dose levels of talimogene laherparepvec (all initial doses were 10^6 PFU/mL, followed by subsequent doses of 10^6, 10^7 or 10^8 PFU/mL) a greater mean decrease in tumor size was observed in patients receiving subsequent doses of 10^7 PFU/mL or higher compared to those administered only 10^6 PFU/mL for all doses. The study also reported that none of the injected tumors in the lowest dose cohort (10^6 PFU/mL) had resolved by the end of the treatment period, whereas 36.5%

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(12/32) of measurable tumors resolved (i.e., were no longer detectable) at the higher dose levels, suggesting that talimogene laherparepvec has a dose-related effect on tumor necrosis.[26] Necrosis of injected tumors, confirmed on histopathology, was observed in both seropositive and seronegative subjects. These data supported the conclusion that an initial dose of 10^6 PFU/mL, followed by doses of 10^8 PFU/mL, was appropriate for use in further trials. This dose regimen has been used in several ongoing phase III of trials including in subjects with advanced stage melanoma.[28]

Clinical data currently available indicate that talimogene laherparepvec has the potential to provide overall clinical benefit to patients with advanced melanoma (Talimogene Laherparepvec Investigator's Brochure, 2012). In particular, a high rate of complete response (CR) was achieved (20% in the phase 2 study with talimogene laherparepvec in stage IIIc to IV melanoma).[29] Response was still ongoing for all but 1 subject at the time of the last tumor evaluation, with a median duration of longest response of 223 days (Talimogene Laherparepvec Investigator's Brochure, 2012). In addition, responses were observed in both injected and uninjected sites, including visceral sites.

In another study, patients with stage III/IVA/IVB squamous cell cancer of the head and neck (SCCHN) were treated with intra-tumoral injections of talimogene laherparepvec in combination with chemoradiotherapy in a phase I/II study. Subjects received chemoradiotherapy (70 Gy/35 fractions with concomitant cisplatin 100 mg/m2 on days 1, 22, and 43) and dose-escalating (10^6, 10^6, 10^6, 10^6 pfu/mL for cohort 1; 10^6, 10^7, 10^7, 10^7 for cohort 2; 10^6, 10^8, 10^8, 10^8 for cohort 3) by intratumoral injection on days 1, 22, 43, and 64. Patients underwent neck dissection 6 to 10 weeks later.

The results from this study are reported in Harrington et al and indicate that seventeen patients were treated without delays to chemoradiotherapy or dose-limiting toxicity. Fourteen patients (82.3%) showed tumor response by Response Evaluation Criteria in Solid Tumors, and pathologic complete remission was confirmed in 93% of patients at neck dissection. HSV was detected in injected and adjacent uninjected tumors at levels higher than the input dose, indicating viral replication. All patients were seropositive at the end of treatment. No patient developed locoregional recurrence, and disease-specific survival was 82.4% at a median follow-up of 29 months (range, 19-40 months).[26]

1.2.2 Talimogene Laherparepvec Safety Experience

An observational registry study is ongoing to investigate the long-term survival and safety of subjects previously treated with talimogene laherparepvec in any study.[27] Preliminary safety data from the completed clinical studies for which adverse event data are available has shown that the most commonly ($\geq$ 10%) occurring adverse events (without regard to causality and including talimogene laherparepvec given in combination with cisplatin and radiation) are nausea, vomiting, diarrhea, chills, pyrexia, fatigue, flu-like symptoms, injection site reactions, and myalgia. Other common ($\geq$ 1% and < 10%) reactions include arthralgia, pain in extremity, cellulitis, headaches, and dizziness. The adverse event profile, therefore, may include events related to talimogene laherparepvec, chemotherapy, radiation, tumor-related signs and

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symptoms, disease progression, and/or a combination of these.[26] Data thus far supports talimogene laherparepvec to be a safe and well tolerated immunotherapy in human subjects.

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.

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

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

1.3 Radiation Therapy in Sarcoma

The benefits of combination therapy with radiation and surgery in significantly improving local control in STS patients are well documented. Preoperative radiotherapy has been shown to significantly improve local disease control, functional outcomes and survival in patients with locally advanced STS.[4-6] Recent review of literature indicates that about 10% of patients will have ≥ 95% tumor necrosis, and about 25% will achieve ≥ 80% tumor necrosis following preoperative radiation therapy alone.[7-8] Further review indicates that only those patients who achieve ≥ 95% tumor necrosis with preoperative radiation have improved local and distant control as well as overall survival.[8] Despite its reported benefits, radiotherapy is associated with a high rate of complications and significant functional morbidity. O'Sullivan et al compared preoperative versus postoperative external beam radiation (EBRT) for resectable extremity STS.

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Long term follow up revealed no statistical difference in local control and cause specific survival, however, preoperative radiotherapy was associated with a significantly higher rate of acute wound complications (35% vs. 17%, p = 0.01) and a lower rate of late Grade 2– 4 fibrosis (32% vs. 48%, p = 0.07).[9-10] Multiple retrospective reviews have similarly found high rates of acute wound complications in sarcoma patients ranging from 25% to 44%.[11–14] These reported high rates of acute and late toxicities support the need for additional research to improve the safety profile of neoadjuvant radiotherapy.

In addition, there is need to improve efficacy of the radiation treatments to achieve higher rates of tumor necrosis, and, to ensure resection of the tumor with clear margins for successful organ preserving treatment of sarcoma.

1.4 Rationale

Immunotherapy has long been discussed as a promising method for the treatment of patients with solid tumors but thus far its exact role in sarcoma remains to be defined. Analysis of sera from sarcoma patients indicate the presence of both humoral and cellular immune responses against cancer-testis antigens commonly associated with sarcoma tumors and sarcoma cell lines, indicating that immune modulation may play a central role in sarcoma-genesis.[15-17] Viruses have been used in the treatment of cancer since the early 20th century.[16] Herpes simples virus type 1 (HSV-1) is a highly lytic virus which infects a wide variety of human cell types and rapidly replicates itself, resulting in cell lysis and inflammation. This replication can be rendered tumor selective through deletion of the HSV-1 gene encoding ICP34.5.[19-20] Talimogene laherparepvec, is a replication-competent, immune-enhanced HSV-1 for intratumoral injection. It is made from a new HSV-1 strain in which the neurovirulence genes encoding ICP34.5 and ICP47 have been deleted. The deletion of ICP34.5 allows for selective replication of the virus in tumor cells. Deletion of ICP47 prevents the inhibition of antigen presentation usually caused by the expression of this protein, and also promotes tumor-selective viral replication. In addition, the ICP34.5-gene has been replaced with the coding sequence for human granulocyte macrophage colony stimulating factor (GM-CSF), to enhance the immune response to tumor antigens released from virus replication.[21-22]

The primary goal of this study is to improve on the 10% of patients who achieve ≥ 95% tumor necrosis historically seen with radiation therapy alone.[7-8] Theoretically, replicating HSV-derived oncolytic agents are sufficient to cause impressive cell killing independent of any interactions with the immune system. Oncolytic HSV-1 elicits an immune response both to the HSV and to tumor-specific antigens. The expressed GM-CSF further stimulates a cytotoxic T cell response against tumor antigens released through viral oncolysis.[21-22] The T-cell stimulation index and the level of immune response may have important correlation with clinical vaccine efficacy, as seen in the phase III trial by Small et al.[30] Additionally, there is growing evidence that radiation induces immunogenic tumor cell death and alters the tumor microenvironment to enhance recruitment of antitumor T cells and, thus, enhancing the overall immune response.

Finkelstein et al recently demonstrated enhanced antitumoral immune response following concurrent administration of dendritic cells and radiation compared to either therapy alone.[23]

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Similarly, synergistic effect between talimogene laherparepvec injection and radiotherapy has been reported in melanoma patients.[24-26] The efficacy and safety of talimogene laherparepvec is most mature in studies involving patients with malignant melanoma, pancreatic, and head and neck cancers. At least nine clinical trials and extended protocols have been or are being conducted with over 400 subjects treated with talimogene laherparepvec.[24-28] An observational registry study is ongoing to investigate the long-term survival and safety of subjects previously treated with talimogene laherparepvec in any study.[27] The most commonly (≥ 10%) reported adverse reactions are nausea, vomiting, diarrhea, chills, pyrexia, fatigue, flu-like symptoms, injection site reactions, and myalgia. Other common (≥ 1% and < 10%) reactions include arthralgia, pain in extremity, cellulitis, headaches, and dizziness. Concurrent therapy with talimogene laherparepvec, cisplatin, and EBRT in a recent phase II study was well tolerated and the adverse events were mostly mild (Grades 1 and 2). The most frequent toxicities and severity in this study were consistent with that seen with conventional chemoradiotherapy.[26] Data thus far supports talimogene laherparepvec to be a safe and well tolerated immunotherapy in human subjects.

2. REGISTRATION PROCEDURES

NA; Single Institution study.

3. OBJECTIVES

3.1 Primary Objectives

Phase 1b: To determine the safety and tolerability of neoadjuvant talimogene laherparepvec in combination with preoperative EBRT as assessed by incidence of dose-limiting toxicities (DLT) in subjects with locally advanced high grade soft tissue sarcomas.

Phase 2: To estimate the efficacy of neoadjuvant talimogene laherparepvec and radiotherapy as assessed by the pathological complete response rates (pCR) in subjects with histologically confirmed diagnosis of locally advanced STS that is unresectable with clear wide margins, for which preoperative radiotherapy is considered appropriate.

For this study, pCR will be defined as ≥ 95% tumor necrosis following concurrent radiation therapy and talimogene laherparepvec.

3.2 Secondary Objectives

- Overall response rate (ORR) as measured by RECIST 1.1 or a later tool for monitoring disease progression.
- Time to progression
- Overall survival rate (OS) at 5 years.
- To further assess the safety of talimogene laherparepvec given concurrently with preoperative external beam radiation in sarcoma patients.

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4. PATIENT SELECTION

4.1 Eligibility Criteria

4.1.1 Subject has provided informed consent.

4.1.2 Histologically confirmed diagnosis of locally advanced STS that is unresectable with clear wide margins, for which preoperative radiotherapy is considered appropriate.

EXAMPLES:

- Resectable stage IIB, III, and IV disease that are not suitable for surgically resection alone due to inability to achieve clear margins.
- Including metastatic (stage IV) disease for which radiotherapy and surgical resection are indicated.
- Except certain histologic subtypes: GIST, Desmoid, Ewing sarcoma, Kaposi sarcoma, and bone sarcomas.

4.1.3 Previous treatment: prior systemic anti-cancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy are allowed provided therapy completed at least 1 year prior to enrollment.

- No prior Talimogene laherparepvec or tumor vaccines allowed.
- No prior radiation to the same tumor bed allowed.

4.1.4 Age ≥18 years.

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

4.1.6 ECOG performance status ≤1.

4.1.7 Patient must have measurable disease:

- Tumor size at least ≥ 5 cm in the longest diameter as measured by CT scan or MRI for which radiation is feasible.

4.1.7.1 Patient must have injectable disease (direct injection or ultrasound guided).

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4.2 Exclusion Criteria

4.2.1 Certain histologic subtypes: GIST, Desmoid, Ewing sarcoma, Kaposi sarcoma, and bone sarcomas

4.2.2 History or evidence of sarcoma associated with immunodeficiency states (e.g.: Hereditary immune deficiency, HIV, organ transplant or leukemia).

4.2.3 Subjects with retroperitoneal and visceral sarcoma.

4.2.4 History or evidence of gastrointestinal inflammatory bowel disease (ulcerative colitis or Crohn's disease) or other symptomatic autoimmune disease including, inflammatory bowel disease, or history of any poorly controlled or severe systemic autoimmune disease (i.e., rheumatoid arthritis, systemic lupus erythematosus, scleroderma, type I diabetes, or autoimmune vasculitis).

4.2.5 History of other malignancy within the past 3 years except treated with curative intent and no known active disease present and has not received chemotherapy for ≥ 1 year before enrollment/randomization and low risk for recurrence.

4.2.6 History of prior or current autoimmune disease.

4.2.7 History of prior or current splenectomy or splenic irradiation.

4.2.8 Active herpetic skin lesions

4.2.9 Require intermittent or chronic treatment with an anti-herpetic drug (e.g., acyclovir), other than intermittent topical use.

4.2.10 Any non-oncology vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment and during treatment period.

4.2.11 Concomitant treatment with therapeutic anticoagulants such as warfarin.

4.2.12 Known human immunodeficiency virus (HIV) disease (requires negative test for clinically suspected HIV infection).

4.2.13 Acute or chronic hepatitis B or hepatitis C infection (requires negative test for clinically suspected hepatitis B or hepatitis C infection).

- Evidence of hepatitis B -
  1. Positive HBV surface antigen (indicative for chronic hepatitis B or recent acute hepatitis B).
  2. Negative HBV surface antigen but positive HBV total core antibody (indicative for resolved hepatitis B infection or occult hepatitis B) and detectable copies of HBV DNA by PCR (detectable HBV DNA copies suggest occult hepatitis B).

- Evidence of hepatitis C -

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1. Positive HCV antibody and positive HCV RNA by PCR (undetectable RNA copies suggest past and resolved hepatitis C infection).

4.2.14 Female subjects who are pregnant or breast-feeding, or planning to become pregnant during study treatment and through 3 months after the last dose of study treatment.

4.2.15 Female subjects of childbearing potential or male subjects who are unwilling to use 2 highly effective methods of contraception during study treatment and through 3 months after the last dose of study treatment. See Section 7.5 for more details.

4.2.16 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(s).

4.2.17 Other investigational procedures while participating in this study that could affect the primary objective of the study as determined by the PI are excluded.

4.2.18 Subject previously has entered this study.

4.2.19 Patients who are receiving any other investigational agents.

4.2.20 Evidence of CNS metastases.

4.2.21 History of allergic reactions attributed to compounds of similar chemical or biologic composition to talimogene laherparepvec.

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

4.2.23 Patients on or requiring immunosuppressive therapies.

4.2.24 Any of the following laboratory abnormalities:

- Hemoglobin < 9.0 g/dL
- Absolute neutrophil count (ANC) < 1500 per mm^3
- Platelet count < 100,000 per mm^3
- Total bilirubin > 1.5 × ULN
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × ULN
- Alkaline phosphatase > 2.5 × ULN
- PT (or INR) and PTT (or aPTT) > 1.5 × ULN
- Creatinine > 2.0 × ULN

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5. TREATMENT PLAN AND STUDY SCHEMA

5.1 Study Design

This is a single-arm open-label phase Ib and phase II clinical study assessing the safety and relative efficacy of concurrent talimogene laherparepvec in combination with radiotherapy in patients with soft tissue sarcomas. Patients will be treated with neoadjuvant radiation and weekly intratumoral injections of talimogene laherparepvec. Weekly injections of talimogene laherparepvec will be continued until surgery. Surgery will be performed 4-6 weeks from the end of radiation therapy to allow for resolution of acute toxicities per current standard of care.

Phase 1b:
The phase Ib portion of this study is to ensure the safety and tolerability of talimogene laherparepvec in combination with EBRT as assessed by incidence of dose-limiting toxicities (DLT). Although this combination has been shown to be safe and well tolerated in several other tumor types including melanoma and head & neck cancers, this combination has not been studied in sarcoma patients. EBRT will be given at the standard dose for resectable soft tissue sarcomas according to the NCCN sarcoma guidelines.[2] Patients will receive 50 Gy over 5 weeks, during which time they will be receiving weekly injections of talimogene laherparepvec. Weekly injections of talimogene laherparepvec will be continued until surgery 4-6 weeks later. Surgery will be performed 4-6 weeks from the end of radiation to allow for adequate tissue healing and resolution of acute toxicities.

Talimogene laherparepvec will be dosed at an initial dose of up to 4.0 mL of 10^6 PFU/mL on day 1 of week 1, followed by the target dose of up to 4.0 mL of 10^8 PFU/mL (Dose 0) three weeks later on day 1 of week 4, and dosed weekly until surgery. Initially 3 patients will be entered at the Dose 0 (following initial dose of up to 4.0 mL of 10^6 PFU/mL on day 1 of week 1) for talimogene laherparepvec and be monitored at this weekly dose through 4 injections, when safety issues will be addressed. If none or one of the 3 patients shows a DLT, three more patients will be entered into the study at this dose and be monitored at this weekly dose through 4 injections. If none or one of these 6 patients shows a DLT, this is the dose that will be used for the phase II relative efficacy assessment. Otherwise, talimogene laherparepvec dose will be deescalated and dose -1 will be explored as outlined below in Table 1. For this protocol DLT will be defined as an attributed adverse event (definite, probable or possible) that meets the criteria in Section 6.2.

Phase 2:
The phase 2 part of the study will provide an estimate of the relative treatment effect of talimogene laherparepvec in combination with preoperative EBRT in subjects with histologically confirmed diagnosis of locally advanced STS that is unresectable with clear wide margins, for which preoperative radiotherapy is considered appropriate, as measured by pathological response rates. Twenty- three (23) patients will be enrolled into the phase 2 portion of this protocol.

As above, patients will receive the first dose of talimogene laherparepvec 4.0 mL of 10^6 PFU/mL on day 1 of week 1, and followed three weeks later by weekly injections at Dose 0. Weekly injections of talimogene laherparepvec will be continued until surgery. The EBRT will be given at the standard dose for resectable soft tissue sarcomas according to the NCCN sarcoma

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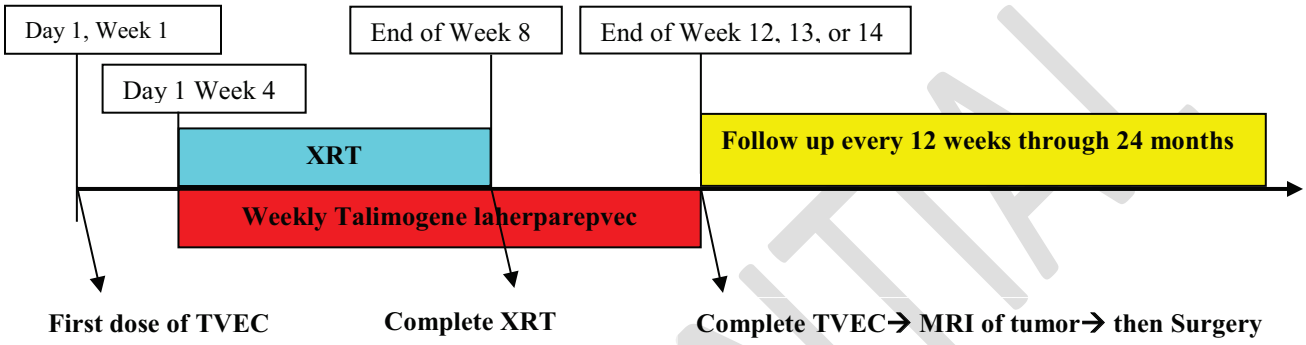
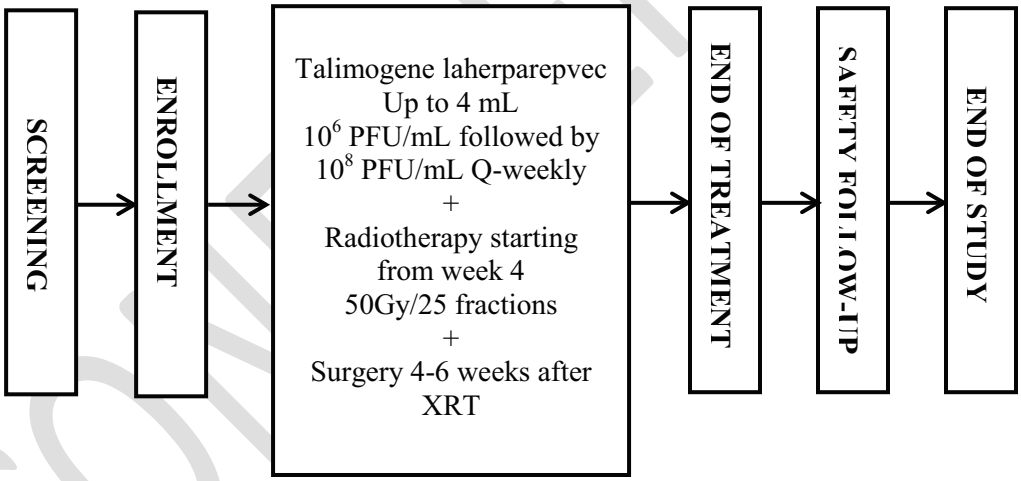
guidelines.[2] Patients will receive preoperative radiation at a dose of 50 Gy over 5 weeks starting around week 4, and continued concurrently with weekly injections of talimogene laherparepvec. Subjects should be followed by clinic visit every 12 weeks for approximately 24 months after the end of the treatment phase, at which time the initial survival data and disease recurrence will be assessed. Subjects will be followed for an additional 3 years for survival and disease recurrence after that according to the standard-of-care. Please see study calendar in Section 10.

Study Timeline Schema:



Phase 1b schema:



Phase 2 schema:

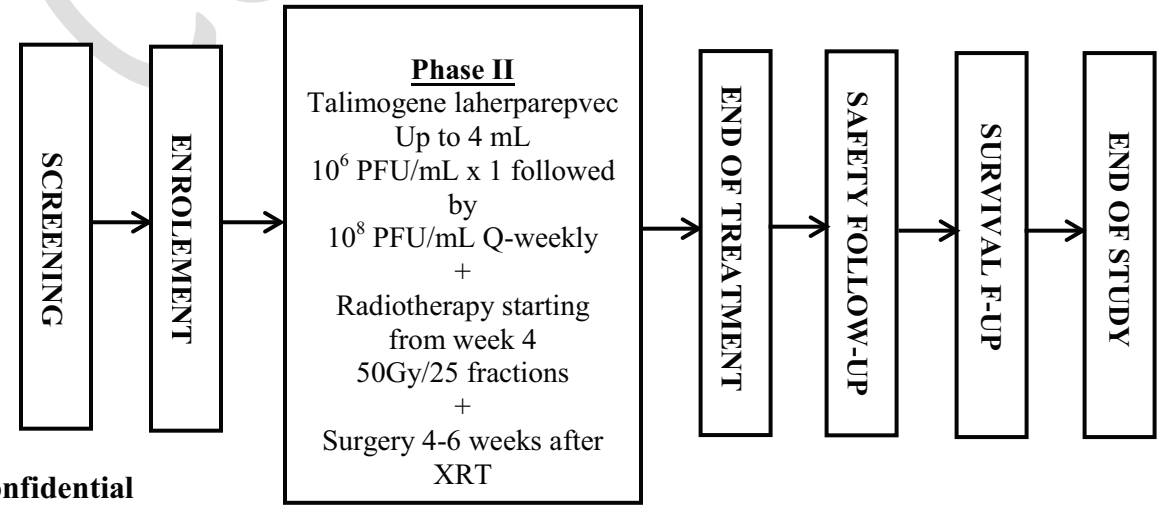


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Table 1.

Number of Patients with DLT at a Given Talimogene Laherparepvec Dose	**Decision Rule**
$\geq$ 2	Dose level will be declared toxic. If this is the lowest dose level, stop the study due to excessive toxicity; otherwise enter *three* additional patients at the next lowest dose level
$\leq$ 1 out of 3	Enter *three* more patients at this dose level
$\leq$ 1 out of 6	This is the recommended dose for the subsequent pilot study

Talimogene Laherparepvec Dose Levels:
Dose 0 = talimogene laherparepvec up to 4.0 mL of 10^8 PFU/mL dosed weekly
Dose -1 = talimogene laherparepvec up to 4.0 mL of 10^8 PFU/mL dosed every 2 weeks.

- Initial dose for all = talimogene laherparepvec up to 4.0 mL of 10^6 PFU/mL

Rationale for Talimogene Laherparepvec Dosing
Multiple studies have documented the efficacy and safety of talimogene laherparepvec in melanoma and head and neck cancer patients.[24-26] In a phase I study to evaluate the safety, bio-distribution, and biological activity of differing dose levels of talimogene laherparepvec in patients with advanced solid tumors, Hu et al identified that subjects who are seronegative for HSV-1 more commonly developed febrile flu-like symptoms and erythematous skin rashes at higher initial doses of talimogene laherparepvec (10^7 and 10^8 PFU/mL) compared to a decreased initial dose of 10^6 PFU/mL.[27] Additionally, in a phase I/II upward-titration study to assess the safety and biological activity of three dose levels of talimogene laherparepvec (all initial doses were 10^6 PFU/mL, followed by subsequent doses of 10^6, 10^7 or 10^8 PFU/mL) a greater mean decrease in tumor size was observed in patients receiving subsequent doses of 10^7 PFU/mL or higher compared to those administered only 10^6 PFU/mL for all doses. The study also reported that none of the injected tumors in the lowest dose cohort (10^6 PFU/mL) had resolved by the end of the treatment period, whereas 36.5% (12/32) of measurable tumors resolved (i.e., were no longer detectable) at the higher dose levels, suggesting that talimogene laherparepvec has a dose-related effect on tumor necrosis.[26] For this study all subjects will be treated with an initial dose of talimogene laherparepvec 10^6 PFU/mL, followed by 10^8 PFU/mL for all subsequent doses in accordance with the currently approved maximum tolerated dosing per the above phase I studies.

5.2 Study Agent Administration: Talimogene Laherparepvec

5.2.1 Talimogene Laherparepvec Dose Levels:

- Initial dose for all = talimogene laherparepvec up to 4.0 mL of 10^6 PFU/mL
- Dose 0 = talimogene laherparepvec up to 4.0 mL of 10^8 PFU/mL dosed weekly
- Dose -1 = talimogene laherparepvec up to 4.0 mL of 10^8 PFU/mL dosed every 2 weeks.

<u>Dosing Schedule:</u>
Patients will be treated with 50 Gy over 5 weeks and concurrent weekly injections of talimogene

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laherparepvec. Weekly injections of talimogene laherparepvec will be continued until surgery, about 4-6 weeks later.

Dosing Information:
Talimogene laherparepvec will be only administered by intratumoral injection into soft tissue tumors with or without image ultrasound guidance. Talimogene laherparepvec must not be administered into visceral organ metastases.

The initial dose of talimogene laherparepvec is up to 4.0 mL of 10^6 PFU/mL. Subsequent doses of talimogene laherparepvec are up to 4.0 mL of 10^8 PFU/mL. The maximum volume of talimogene laherparepvec administered at any dose is 4.0 mL for any individual lesion. The maximum dose in any one treatment is 4.0 mL. Investigators are encouraged to use the maximum amount whenever lesions allow. In response to severe AEs, dose delays and dose de-escalations may be employed, but dose volume reduction for AEs is not allowed – see Section 6. However if in the course of administration of talimogene laherparepvec the subject cannot tolerate the full dose due to an injection-related AE such as pain, the total volume given should be recorded, and the reason for intolerance should be documented as an AE.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.2.2 Lesion site preparation

- Talimogene laherparepvec is only to be administered by intralesional injection into soft tissue tumors with or without image ultrasound guidance. Talimogene laherparepvec must not be administered into visceral organ metastases.
- The injection site may be pre-treated with a topical anesthetic agent or an injectable local anesthetic; however, a local anesthetic must not be injected directly into the lesion.
- Swab the lesion and surrounding areas with alcohol, allow to dry.

5.2.3 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 is recommended; multiple insertion points may be used if the tumor is larger than the radial reach of the needle.
  b) Talimogene laherparepvec should be injected along multiple different tracks within the lesion in order to obtain as wide a dispersion as possible.
  c) Distribute talimogene laherparepvec within the lesion through the insertion point using the radial reach of the needle in different directions to evenly distribute.

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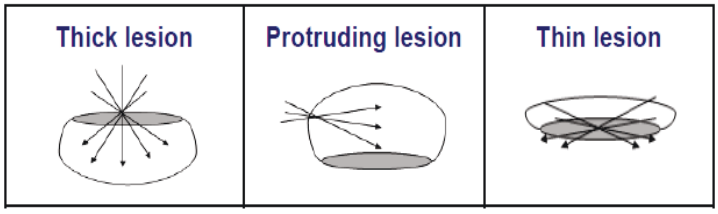

- Avoid premature extraction of needle.
- After dosing, the injection site should be swabbed with alcohol and pressure should be applied with gauze for several seconds after injection.
- The injection site should be covered with an absorbent pad and dry occlusive dressing.
- Dispose materials used during injection (e.g., gloves, needles, gauze) in accordance with local/regional and institutional requirements for biohazardous waste.

5.2.4 Radiation Therapy

External beam radiation therapy will be given at the standard dose for resectable soft tissue sarcomas according to the NCCN sarcoma guidelines.[2] Patients will receive 50 Gy over 5 weeks, during which time they will be receiving weekly injections of talimogene laherparepvec. Weekly injections of talimogene laherparepvec will be continued until surgery 4-6 weeks later. Surgery will be performed 4-6 weeks from the end of radiation to allow for adequate tissue healing and resolution of acute toxicities.

Radiation therapy for this protocol is as per currently used standard pre-operative radiation therapy at the University of Iowa even for non-protocol patients.
Selected guidelines from previously conducted Radiation Therapy Oncology Groups (RTOG) studies are briefly summarized for this protocol.

Preoperative Radiation therapy (3D-CRT or IMRT)
Either 3D conformal radiotherapy or intensity modulated radiation therapy may be utilized for adequate tumor coverage and to meet the dose constraints for critical normal structures.

Radiation treatment planning scans and immobilization:
CT scans with patient in a stable and comfortable position will be used for planning. MRI scans are optional and may be used for co-registration with CT for tumor localization as needed. VacLoc or other immobilization devices can be used for immobilization.

Target volumes and treatment field:
Gross Target Volume (GTV): Outline of the tumor as seen on CT or CT/MRI fusion.
Clinical Target Volume (CTV): CTV = GTV plus 4 cm margins in the proximal and distal directions. However the margin can be reduced if it extends beyond the compartment, the field can be shortened to include the end of a compartment. The radial margin from the lesion should be 1 cm. It can be reduced in areas confined by the fascial barrier or bone or skin surface.
Planning Target Volume (PTV): Include CTV and error of setup and organ motion. Typically PTV includes CTV plus 1 cm in all dimensions. Final PTV is usually GTV + 5 cm longitudinal and 2 cm radial, except where restricted by the compartment end, fascia, bone or skin surface.

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Use of bolus on the skin surfaces is optional as needed. Where applicable, biopsy scars should be bolused with appropriate thickness specific to the energy of the photon beam.

Dose Specifications:
A dose of 50 Gy in 25 daily fractions will be prescribed to the planning target volume (PTV) using linear accelerator and megavoltage photon beams with energies of 6MV or greater. Prescribed dose should cover > 90% of the PTV. More than 95% of the PTV should receive > 95% of the prescribed dose. No more than 20% of the PTV will receive ≥ 110% prescription dose.

Precautions and Dose Constraints for critical structures:
Radiation dose to normal tissues should be kept within the accepted normal tissue tolerances. Every effort should be made to:
a) Avoid treating the full circumference of an extremity;
b) Avoid treating anus, urogenital tract, perineum and genitalia; if the tumor is close to these structures, typically less than 50% volume of the anus and vulva should receive 30 Gy; less than 50% volume of the testis should receive 3 Gy, if the patient prefers to reserve fertility;
c) Avoid treating the lung, through use of appropriate shielding and treatment planning; less than 20% of the lungs should receive 20 Gy (V20);
d) Avoid dose maximums in areas where surgical scars will be placed; this may require reviewing treatment plans with the surgeon;
e) If possible, avoid treating skin over areas commonly traumatized to full dose (e.g., the elbow, knee, shin, femoral neck).
f) If possible, less than 50% of any joints (including shoulder, elbow and knee) should receive 50 Gy.
g) Less than 50% of kidney volumes should receive 18 Gy.
h) No more than 50% of normal weight-bearing bone within the radiation field should receive 50 Gy except when the tumor invades the bone or when there is circumferential involvement of the tumor more than a quarter of the bone or when the bone will be resected in a subsequent surgical resection after radiation.
For any other normal tissue structures, no radiation dose more than the established TD5/5 limit should be given.

Image Guidance and Verification Devices
Portal films or conebeam CT images should be used for target localization and alignment. Daily conebeam CT will be preferred and dose from daily conebeam should be included in the final dosimetry.

Postoperative Radiotherapy Boost
External Beam or Brachytherapy boost can be given at the discretion of the radiation oncologist, to the positive tumor margin (residual tumor) only plus a margin of 1 cm within 2 weeks following surgery or after adequate wound healing has occurred.
The target volume for postoperative radiotherapy will be the residual tumor bed as defined by the surgical and pathological findings.

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External Beam Radiotherapy
Postoperative external beam boost dose is 16 Gy in 8 fractions (once a day).

Brachytherapy
High-dose-rate (HDR) brachytherapy as a boost to the positive tumor margin can be used as an alternate to external beam radiotherapy. Brachytherapy catheters are placed at an interval of 0.5 -1.0 cm on the residual tumor bed (positive margin) plus a margin of 1 cm during surgery. Skin surface dose should be kept below 50% of the prescription dose unless positive margins occur in cutaneous or subcutaneous tissues. It is not necessary to include the entire surgical bed, drain sites and wound. Brachytherapy should not start until day 5 after the surgery (day 0) and must be completed within 2 weeks following surgery.
For HDR brachytherapy, 4 fractions of 3.4 Gy are delivered b.i.d, with an interval of at least 6 hours between fractions.

Radiation Therapy Adverse Events
Acute: Wound complications of any grade are expected to develop in about one third of patients. Other common radiation adverse events include: fatigue, regional alopecia, diarrhea, skin erythema and desquamation within the treatment fields, and reduction in blood counts.
Long-term: Common long-term treatment adverse events include: lymphedema of the extremity receiving radiation and surgery, subcutaneous fibrosis, and joint stiffness. Much less common radiation adverse events include bowel injury, osteoradionecrosis, and bony fracture in the radiation field. There also is a risk of secondary malignancy occurring in the irradiated field.

5.3 General Concomitant Medication and Supportive Care Guidelines

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded.

All other protocol-required therapies including, topical anesthetic or an injectable local anesthetic medications used for pretreatment of the talimogene injection site and oral or systemic treatments required for management of immune-mediated AEs that are to be obtained commercially.

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. All prescription and nonprescription concomitant medication administered up to 28 days prior to enrollment, on an ongoing basis at enrollment, as well as changes in such concomitant medication, and any new concomitant medication taken while the subject is on study, should be recorded up to 30 days after the last dose of talimogene laherparepvec.

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5.4 Duration of Therapy

Concurrent immunoradiotherapy with a total of 50 Gy of radiation and weekly talimogene laherparepvec intratumoral injections will be given over 5 weeks. Then, weekly intratumoral injections of talimogene laherparepvec will be continued until surgery is performed around 4-6 weeks later. In the absence of treatment delays due to adverse event(s), treatment may continue until surgical resection of the tumor, or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.5 Duration of Follow Up

Safety Follow up Visit

Upon permanent discontinuation from the study treatment for any reason, the following procedures will be performed approximately 30 (+7) days after the last dose of Talimogene Laherparepvec:

- Recording of concomitant medications and AE/SAE(s)
- Physical examination including weight, vital signs and ECOG performance status assessment
- Local laboratory tests including the following:
    - Hematology panel
    - Chemistry panel
    - Serum or urine pregnancy test for female subjects of childbearing potential

Long-term Follow up

Following the end of treatment, subjects will be followed according to standard of care (approximately every 12 weeks), at the discretion of the treating physician, at which time disease recurrence and survival status will be assessed for up to 5 years. Data for disease recurrence and survival status only will be collected per chart review, phone call or email.

End of Study

The end of study for each subject is defined as the date the subject withdraws full consent from the study, completes the safety follow-up visit or the long-term survival follow-up whichever is later, or death.

5.6 Criteria for Removal from Study

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Talimogene laherparepvec is to be permanently discontinued for subjects meeting any of the following criteria:

- The subject, for any reason, requires treatment with another anticancer therapeutic agent for treatment of the study disease (other than the exceptions noted in protocol, if applicable). In this case, discontinuation from the treatment occurs immediately upon introduction of the new agent.
- Clinical relevant disease progression as defined in the study protocol.
- Immune-mediated adverse events have been observed in subjects receiving talimogene laherparepvec. These have included pauci-immune glomerulonephritis, vasculitis, and pneumonitis; however, immune-mediated adverse events can potentially involve any organ system. Permanently discontinue talimogene laherparepvec if dosing is delayed by more than 4 weeks due to a Grade 2 or greater immune-mediated adverse event (with the exception of vitiligo), allergic reactions, or urticaria attributed to talimogene laherparepvec.
- Plasmacytoma has been observed with the administration of talimogene laherparepvec. Permanently discontinue talimogene laherparepvec if development of a plasmacytoma is observed.
- Any talimogene laherparepvec-related non-hematologic or hematologic toxicities Grade 3 or greater that, in the opinion of the investigator, would require a dose delay of greater than 4 weeks (approximately 6 weeks from the previous dose) or discontinuation of therapy.
- A female subject becomes pregnant or fails to use 2 highly effective methods of contraception (for those subjects who are able to conceive).
- A female subject breast feeds while on study treatment.
- A male subject fails to use a highly effective method of contraception as described in Section 7.5.
- Intercurrent medical illness that, in the judgment of the investigator, would make continued treatment with talimogene laherparepvec dangerous for the subject.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Delays

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 dose-limiting toxicities occur, talimogene laherparepvec administration should be delayed until the DLT has resolved to at least CTCAE version 4.0 Grade 1 (see Appendix E). Dosing of talimogene laherparepvec could also be delayed for active herpetic cutaneous or mucosal lesions, herpes labialis, or active dermatoses in the region of the injected tumors. Talimogene laherparepvec should be discontinued for subjects with evidence of systemic herpetic infection, herpetic keratitis, encephalitis, or evidence of other disseminated herpetic infection or any herpetic infection requiring treatment with acyclovir or a similar agent.

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

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

6.2 Dose Limiting Toxicities

Definitions of dose-limiting toxicity:
Toxicity will be evaluated according to CTCAE version 4.0. DLT will be defined as any of the following talimogene laherparepvec-related toxicity or related to the combination of talimogene laherparepvec and radiation therapy during treatment and up to 4 weeks after the last talimogene laherparepvec injection:

- Grade 3 or greater immune-mediated adverse events
- Grade 3 or greater allergic reactions.
- Any grade plasmacytoma
- Any other unexpected grade 3 or greater hematologic or non-hematologic toxicity, with the exceptions of:
  - Any grade of alopecia.
  - Expected radiation related skin toxicity of any grade.
  - Grade 3 arthralgia or myalgia.
  - Brief (< 1 week) grade 3 fatigue.
  - Grade 3 fever.
  - Grade 3 diarrhea or vomiting responding to supportive case.

Of note, unless an alternative etiology has been identified, signs and symptoms of any disease process described above as a DLT should be considered immune-mediated.

If unexpected DLT occurs, talimogene laherparepvec administration should be delayed until the DLT has resolved to at least CTCAE version 4.0 grade 1. If dosing is delayed by more than 4 weeks due to the occurrence of unexpected adverse event that is considered related to talimogene laherparepvec, then the subject should be taken off treatment.

6.3 Dose Reductions

Dose reductions with regards to changes in the concentrations of talimogene laherparepvec are not permitted.

- Patients may require a reduction in the volume injected due to a disease response as outlined in Section 5.1.

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- Additionally, subjects who miss two consecutive doses of talimogene laherparepvec due to a DLT should be reduced to a biweekly dosing (dose -1 as in section 5.1).

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

Information regarding the occurrence of adverse events will be collected from the time the subject signs the informed consent form and throughout their participation in the study, including a period of 30 days after the last dose of study drug (data on serious adverse events (SAEs) will be collected until resolution of the event unless otherwise noted). Serious adverse events occurring outside the 30-day follow-up period, which are assessed as related to study drug, should be reported to Amgen, along with any SAE that the investigator feels should be reported.

7.1 Adverse Event Definitions

An **adverse event** (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, without any judgment about causality. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

Following surgical resection of the tumor, non-serious adverse events consistent with an expected post-operative course will not be reported unless attributable to the study drug and/or meet the seriousness criteria.

An adverse event is considered a **serious adverse event** (SAE) if it results in any of the following outcomes:

1) Results in death
2) Is a life-threatening event (ie, its occurrence places the patient or subject at immediate risk of death)
3) Requires inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) Is a congenital anomaly/birth defect
6) Is an important medical event that may not result in death, be life threatening, or require hospitalization but may be considered serious when, based upon medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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Suspected Adverse Reaction
Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected Adverse Events
An adverse event is considered "unexpected" if it is not listed in the table of expectedness within the Investigator Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

When talimogene laherparepvec is administered in combination with 1 or more approved antineoplastic agents, the expectedness determination should take into account the labeling of each specific marketed drug taken in combination based upon reference documents which will be included or referenced in the clinical study protocol. The labeled events should, in general, be considered expected for at least one of the drugs in the combination. The contribution of talimogene laherparepvec to the severity or frequency of the events is currently unknown.
See Section 1.2.2 for adverse drug reactions that could be reasonably assumed to be associated with talimogene laherparepvec.

7.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix E) will be utilized for AE reporting. If specific grading is not available in the CTCAE for a particular AE's severity/intensity, the Investigator is to revert to the general definitions of Grade 1 through 5 and use his/her best medical judgment. The 5 general grades are: Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life-threatening or disabling, Grade 5 = death related to AE.

Attribution of the AE:
Investigators are required to assess whether there is a reasonable possibility that talimogene laherparepvec caused or contributed to the adverse event. The following general guidance may be used.

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Comprehensive Adverse Events and Potential Risks List (CAEPR)

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All necessary supportive care shall be available to subjects. Additional treatment modifications should be considered depending upon the subject's clinical situation. Talimogene laherparepvec treatment should be continued based on the potential risk/benefit assessment of the subject.

7.3.1 Important Identified Risks

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.

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. Subjects should be monitored closely for cellulitis and injection site reactions.

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

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(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.

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.

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.

Other important identified risks include obstructive airway disorder and deep vein thrombosis.

7.4 Important Potential Risks

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 107 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

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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.

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 1 hour 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.

Symptomatic Herpetic Infection Due to Latency and Reactivation of Talimogene Laherparepvec or Wild-type HSV-1 in Patients

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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.

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.

Impaired Wound Healing at Site of Injection
The local tissue response following repeated injections of a foreign protein can contribute to

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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. All subjects should be monitored very closely for impaired wound healing especially in the setting of concurrent use of radiation therapy.

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 (Section 7.2.3).

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.

Other Relevant Information
Refer to the DCSI attached to this brochure as Appendix D for a description of current information related to adverse drug reactions, special warnings and precautions, contraindications, and risks for overdoses with talimogene laherparepvec.

7.5 PREGNANCY AND BREASTFEEDING

Pregnancy
No studies of the effects of talimogene laherparepvec on reproduction and development have been performed in humans. Talimogene laherparepvec should not be used during pregnancy.

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Females:
Pregnant women and women planning to become pregnant should not receive talimogene laherparepvec. Women who can become pregnant must use 2 highly effective birth control methods (either by her alone or in combination with her male partner) during treatment with talimogene laherparepvec and for at least 3 months after the last tumor injection of talimogene laherparepvec. Highly effective methods of contraception include:

- Use of hormonal birth control methods: pills, shots, implants (placed under the skin by a health care provider) or patches (placed on the skin)
- Intrauterine devices (IUDs)
- Sexual activity with a male partner who has had a vasectomy (surgery to become sterile)
- Prior surgery to tie her fallopian tubes (surgery to become sterile)
- Condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicide

If a woman becomes pregnant or suspects she is pregnant, she must tell her doctor immediately and treatment with talimogene laherparepvec will be stopped. The study doctor should notify Amgen of the pregnancy, discuss any follow-up with the subject, and ask for information on the pregnancy outcome.

Males:
The potential for talimogene laherparepvec to be transferred via semen and its effect on sperm are unknown. Males with partners of childbearing potential, must agree for the duration of the treatment with talimogene laherparepvec and continuing for 3 months after the last tumor injection of talimogene laherparepvec to practice a highly effective method of birth control,(either by him or his female partner). Highly effective methods of contraception include:

- Use of hormonal birth control methods: pills, shots, implants (placed under the skin by a health care provider) or patches (placed on the skin)
- Intrauterine devices (IUDs)
- Sexual activity with a male partner who has had a vasectomy (surgery to become sterile)
- Prior surgery to tie her fallopian tubes (surgery to become sterile)
- Condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicide

If a pregnancy occurs, the study doctor must be notified. The study doctor should notify Amgen of the pregnancy, discuss any follow-up with the subject (and/or his partner), and ask for information on the pregnancy outcome. If the female partner is already pregnant when the male subject begins treatment with talimogene laherparepvec, he must refrain from any sort of sexual activity that could expose his partner or the unborn baby to talimogene laherparepvec through semen, or wear a condom during sexual activity while receiving treatment with talimogene laherparepvec and for at least 3 months after the last tumor injection of talimogene laherparepvec.

Breast Feeding*:*
Amgen has not tested whether talimogene laherparepvec is present in breast milk nor assessed the effects of talimogene laherparepvec in breast-fed infants. Therefore, babies should not be fed breast milk produced during treatment with talimogene laherparepvec or for an additional 3 months after the last tumor injection of talimogene laherparepvec.

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7.6 Other Relevant Information

Refer to Appendix D of this document and the DCSI in the latest version of the talimogene laherparepvec Investigator's Brochure for a description of current information related to contraindications and risks for overdoses with talimogene laherparepvec as well as information on the use of talimogene laherparepvec in special subject groups such as pregnant or breast feeding, pediatric, or geriatric populations.

7.7 Expedited Adverse Event Reporting

7.7.1 Expedited Reporting Guidelines

Reporting to the HCCC DSMC

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of the talimogene laherparepvec.

All serious adverse events must be reported to the DSMC within the timeframes detailed below.

Hospitalization	Grade 1 and Grade 2	Grade 3-5
Resulting in inpatient hospitalization	10 calendar days	1 business day initial; 5 calendar day report
Not resulting in inpatient hospitalization	Not required	

<u>Expedited AE reporting timelines are defined as:</u>

- "1 business day; 5 calendar days" - The AE must initially be submitted electronically using OnCore within 1 business day of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial notice.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted electronically via OnCore within 10 calendar days of learning of the AE.

Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 SAEs

Expedited 10 calendar day reports for:

- Grade 2 SAEs resulting in hospitalization or prolongation of hospitalization

<u>Serious Adverse Events</u>

An adverse event is considered serious if it results in ANY of the following outcomes:

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1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

The investigator is responsible for ensuring that all SAEs observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 (+ 7) days after the last dose of talimogene laherparepvec are submitted to institutional IRB and FDA. The SAE must be submitted to IRB within 10 working days following the investigator's knowledge of the event via the Reportable Event Form (REF) in HawkIRB.

Reporting Requirements

Safety Reporting to Amgen

The Sponsor/Investigator is responsible for compliance with expedited reporting requirements for serious, unexpected and related adverse events (SUSARs), for generation of SAE reports including narratives, and for periodic reporting to Amgen of SAEs as outlined in Table 2 and Table 3 below. Individual safety reports (Table 2) should be accompanied by the Fax Cover Form and sent to Amgen Global Safety, utilizing the fax of email information provided on the cover page. Aggregate safety reporting (Table 3) including listings, tabulations and summary reports should be scanned and accompanied by the Fax Cover Form and sent to Amgen NASCR, utilizing the email information provided on the cover page.

In addition to the requirements outlined in Table 2 and 3, Sponsor/Investigators are required to report **direct exposures** to talimogene laherparepvec (e.g., needle stick, splash back) of herpetic illness and **all suspected herpetic events** (refer to Section 'Accidental Exposures to Talimogene Laherparepvec and Herpetic Events').

Table 2. 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-

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@amgen.com.

Table 3. Aggregate Reports:

Safety Data	Timeframe for Submission to Amgen
Adverse events (all serious and non-serious adverse events, regardless of relatedness)	Line listing and summary tabulation of all adverse events sent annually AND at end of study
US IND Annual Safety Report	Annually
Other Aggregate Analyses (any report containing safety data generated during the course of the study)	At time of ISS sponsor submission to any body governing research conduct (e.g., RA, IRB, etc.)
Final (End of Study) Report, including: • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	At time of ISS sponsor submission to any body governing research conduct (e.g., RA, IRB, etc.) but no later than 1 calendar year after study completion

Aggregate reports should be submitted via email to the Amgen NASCRT manager, accompanied by the Fax Cover Form.

Please refer to the ICH Guidelines E2A for safety related definitions and terminology: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf.

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 4 'Accidental Exposure and Herpetic Event Reporting Requirement Summary.' 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

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 4.

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

o **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.

o **Reporting Process for HCPs and Close Contacts:**

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

Table 4. Accidental Exposure and Herpetic Event Reporting Requirement Summary

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

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herpetic lesions			event	of appearance of symptoms)			
Close Contact (eg caregiver, spouse, child) **with suspected herpetic lesions**	Close Contact's Personal Physician or Close Contact	Within 24 hours of Reporter awareness	Contact Amgen at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions (ideally within 3 days of appearance of symptoms)	Yes, if consent obtained	Close Contact's Personal Physician	Close Contact's Personal Physician and Amgen
*The laboratory conducting the qPCR testing on behalf of Amgen is Viracor.							

Reporting to the FDA

It is the responsibility of the IND sponsor-investigator to comply with IND safety reporting as set forth in the Code of Federal Regulations, Section 312.32. This responsibility includes providing an annual IND report to the FDA. In addition:

- The FDA will be notified via phone (800-332-1088) or fax (800-FDA-0178) within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life- threatening.

- The FDA will be notified via fax (800-FDA-0178) or online submission (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf) with a MedWatch (3500A or 3500) within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but not fatal or life-threatening. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DSMC).

MedWatch 3500a Reporting Guidelines:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm2007307.htm

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500a form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics

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- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

8. PHARMACEUTICAL INFORMATION

8.1 Study Drug: Talimogene Laherparepvec

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

- Talimogene laherparepvec at nominal concentration of 10^6 plaque forming units (PFU)/mL with approximately 1.15 mL in a 2 cc vial for the initial dose
- Talimogene laherparepvec at nominal concentration of 10^8 PFU/mL with approximately 1.15 mL in a 2 cc vial for the second and subsequent doses

8.1.1 Packaging and Formulation of Investigational Product

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

Vials will be sealed with rubber stoppers, Fluorotec-coated on the product side. The vial 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.

8.1.2 Drug storage

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

Table 2. Acceptable Storage Temperature

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

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

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8.1.3 Agent Ordering and Agent Accountability

Sponsors of clinical studies are required to establish a record of receipt, storage, use and disposition of all talimogene laherparepvec used to conduct a clinical study. The Sponsor of the clinical study is responsible for ensuring that accountability is maintained and accurate at each clinical site where the study is conducted. At study activation or as required, initial shipments of talimogene laherparepvec 10^6 PFU/mL and 10^8 PFU/mL concentrations will be shipped to the contact and address provided by the Study Sponsor. It is the responsibility of the Study Sponsor to maintain the records of talimogene laherparepvec accountability in accordance with ICH GCP.

Complete study drug information (including packaging, labeling, ordering, storage and disposition) is provided in the Talimogene laherparepvec Pharmacy Information Guide.

9. CORRELATIVE, AND SPECIAL STUDIES

The underlying hypothesis driving this clinical trial is that the induction of high titers of antibody by intra-tumoral talimogene laherparepvec will result in enhanced tumor recognition by the immune system, and subsequently leading to improved disease control. Patients treated on this study will undergo evaluation of immune response to treatment, including serologic response, and evaluation of the baseline and post-treatment cytokine profile and inflammatory response.

The results will be used to correlate response to vaccination with subsequent clinical outcome.

Blood Samples:
Patient serologic and inflammatory response will be measured at baseline during Screening and prior to the Visit Week 1 injection of the study drug, and immediately preceding injections at Visit Weeks 4, 7, 10, 12 and 18 (+/- 1 week).

With each collection, 1 Red top tube and 1 Green top tube for serum and mononuclear cells (MNC) will be collected for the following tests:

- Cytokine Profile: IL-1*β,* IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, TNF-alpha, IFN-gamma, IFN-alpha, GM-CSF.
- HSV serology.
- NK-cell functional assay.

Tumor Tissue Samples:
The tumor biopsy samples will be used to study the relationship between the immune response induced by talimogene laherparepvec and clinical response or resistance to talimogene laherparepvec. Tumor slides will be systemically analyzed at baseline and post-treatment to evaluate changes in the number and/or type of immune cells infiltrating the tumor during treatment. The protocol may be modified to include analysis of the immune and cancer cells in the tumor to identify ribonucleic acid transcripts and/or proteins whose levels change with treatment, and to assess tumor specific mutations or epigenetic changes.

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- As described above a pre-treatment biopsy sample must be obtained within 3 months from the initiation of treatment.

- The biopsy sample will be assessed for baseline tumor infiltrating lymphocytes (TILs) by the same pathologist. This will include CD3, CD4, CD8, CD56, and FOXP3 positive cells.

- Post treatment TILs, as above, will be assessed on the resected tumor at the end of treatment.

Additionally, blood samples and tumor samples may be saved for any potential additional or future analyses such as tumor specific mutations or epigenetic changes (eg, somatic mutations) on tumor tissues.

The study may be amended to include additional testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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10. STUDY CALENDAR

10.1 Study Procedures

	Study Treatment (week number)[a]															
Study Procedures	**Screen-ing**	**1[i]**	**2**	**3**	**4[i]**	**5**	**6**	**7[i]**	**8**	**9**	**10[i]**	**11**	**12[i]**	**Surgery (wks 12-14)**	**End of Treat-ment[i]**	**Long-term follow up [h]**
General Assessments																
Progress Note	X	X			X	X	X	X	X	X	X	X	X		X	
Recording of Concomitant Medications	X	X			X	X	X	X	X	X	X	X	X		X	
Vital Signs [b]	X	X			X	X	X	X	X	X	X	X	X		X	
Physical Exam, including weight	X	X			X	X	X	X	X	X	X	X	X		X	
ECG	X															
ECOG Performance Status	X	X			X	X	X	X	X	X	X	X	X			
Review of AEs & SAEs [c]		X			X	X	X	X	X	X	X	X	X		X	
Talimogene laherparepvec injection [j]		X			X	X	X	X	X	X	X	X	X			
Correlative labs [i]		X			X			X			X		X		X	
Radiation					X	X	X	X	X							
Survival Status/Disease Recurrence																X
Local Laboratory Tests [d]																
Pregnancy (serum or urine)	X														X	
Chemistry [d]	X	X			X	X	X	X	X	X	X	X	X		X	
CBC, differential, Platelets [d]	X	X			X	X	X	X	X	X	X	X	X		X	
Coagulation (PT or INR and PTT or aPTT)	X															
AST, ALT, AlkPhos, Bili, Albumin[d]	X	X			X	X	X	X	X	X	X	X	X		X	
Thyroid Function Tests	X															
Clinical & Radiographic Tumor/Response Assessments																
Tumor biopsy	**Must be biopsy confirmed within 3 months prior to study enrollment**															
Primary Tumor Assessment (MRI/CT)[e, g]	X												X			
CT Chest, Abdomen, and Pelvis [f]	X												X		X	

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a. Assessments will occur on Day 1 (+/- 3 days) of the week number.
b. Blood pressure, resting pulse, respiration rate, and temperature.
c. All serious adverse events (SAEs) will be reported within 24 hours of the discovery of the event.
d. May be monitored more frequently if indicated.
e. Tumor assessment will be documented per RECIST.
f. CT chest, abdomen, and pelvis at screening (up to 28 days prior to initiation of treatment), Weeks 12 and 18 (+/- 2 weeks), and then standard of care for up to 5 years, at discretion of treating physician.
g. Primary tumor (MRI/CT) at screening (up to 28 days prior to initiation of treatment) and on Day 1 week 1 (or up to 28 days prior and before initiation of treatment) and on Day 1 week 12 (± 2 weeks).
h. Follow up per standard of care (approximately every 12 weeks), at the discretion of the treating physician. Data for survival status and disease recurrence only will be collected.
i. Correlative labs for serologic and inflammatory response; 1 Marble Red top and 1 Green top. See Section 9 (+/- 7 days).
j. Talimogene laherparepvec will be given weeks 1 through 12 (+/- 2 weeks) when surgery is expected to be performed. The injections must be given the same day of the week +/- 3 days.

10.2 Screening Procedures:

- Procedures to be completed within 28 days of enrollment/randomization and prior to first treatment (unless otherwise noted).
  - Informed Consent
  - Review of eligibility criteria
  - Recording of medical history and concomitant medications
  - Physical Exam (including weight)
  - ECG
  - Vital Signs (Blood pressure, resting pulse, respiratory rate, temp.)
  - Radiographic imaging (Chest, abdomen, and pelvis and all other sites of disease)
  - Imaging of primary tumor site

- Laboratory Assessments
  - Within 28 days of enrollment and prior to first treatment.
    - HIV test: Required if clinically indicated
    - Hepatitis B and/or C tests: Required if clinically indicated
  - ≤ 10 days of enrollment
    - Hematology panel (with 5 part differential). 3 part differential if 5 part unable to be performed.
    - Chemistry panel
    - Coagulation panel
    - Thyroid function tests
  - ≤ 3 days of enrollment
    - Serum or urine pregnancy test for females of childbearing potential

10.3 Long-term Follow up

After the end of treatment visit is completed, subjects will be followed according to standard of care (approximately every 12 weeks), at the discretion of the treating physician, at which time disease recurrence and survival status will be assessed for up to 5 years. Data for disease recurrence and survival status only will be collected per chart review, phone call or email.

11. MEASUREMENT OF EFFECT

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11.1 Pathologic Response

At the end of the neoadjuvant therapy, patients will undergo resection of the treated tumor. The pretreatment biopsy and all the resected tumor samples must be reviewed by the same pathologist.

- The percentage of post treatment tumor necrosis must be documented. The primary end point for this study is pathologic complete response (pCR), and is defined as ≥ 95% tumor necrosis following concurrent radiation therapy and talimogene laherparepvec.

- Additional immunohistochemical studies will be performed as described in Section 9.

11.2 Time to Disease progression (TTP)

TTP is defined as the time from Enrollment until objective tumor progression including local and distant recurrences.

11.3 Other Response Parameters

The following response assessment guidelines may be amended during the course of the study if changes are made to the current RECIST Guidelines or if a new disease assessment tool becomes available.

Response Measurement Criteria:

- Measurements of the tumor in its largest dimension should be obtained at baseline and at the end of the treatment phase, prior to surgical resection.
- Response criteria should be by RECIST.
    - Complete response is the disappearance of all target lesions.
    - Partial response is a 30% decrease in the sum of the longest dimensions of the target lesions, relative to baseline.
    - Progressive disease is an increase of 20% or more in the sum of the longest dimension of target lesions
    - Stable disease is a decrease in the tumor size of < 30% or an increase of < 20%.
- Antitumor response by pathologic assessment will be performed on the resected tumors.
- Pathologic assessment will be performed per institutional guidelines.
    - The percent of tumor necrosis and the percent of tumor-infiltrating lymphocytes will be documented.
    - Complete pathological response will be considered ≥ 95% pathologic tumor necrosis.

Radiologic response will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Please see Appendix B for more details of the RECIST Guidelines.

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12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

Phase Ib
The goal of this safety component is to confirm that the current standard dose (neoadjuvant administration of concurrent talimogene laherparepvec and external beam radiation therapy) used for melanoma patients is well tolerated within this population of sarcoma patients as well. Three (3) patients will be recruited for this standard dose. If none of the three patients shows DLT, this dose will be used for the phase II relative efficacy assessment; otherwise, patients dose will be deescalated according to the procedure stated in the investigator brochure (dose -1 and dose -2 will be explored).

Phase II
The endpoint of our phase II component of the study is the proportion of subjects with pathologic tumor necrosis ≥95%. This proportion has been roughly hypothesized to 10% under standard care.

The optimal two-stage design to test the null hypothesis that P≤0.120 versus the alternative that P≥0.350 has an expected sample size of 13.13 and a probability of early termination of 0.705. If the neoadjuvant administration is actually not effective, there is a 0.041 probability of concluding that it is. If it is actually effective, there is a 0.196 probability of concluding that it is not (the target for this value was 0.200). After testing the concurrent administration on 9 patients in the first stage, the trial will be terminated if 1 or fewer respond (i.e. if 0 or 1 patient have pathologic tumor necrosis ≥95%). If the trial goes on to the second stage, a total of 23 patients will be studied. If the total number responding is less than or equal to 5, the neoadjuvant administration will be rejected.

P1	P2	Stage 1	Total	Futility Threshold	Type I	power
.12	.35	9	23	1 and 5	0.041	80%

Data Analysis and Reporting
As described in section 3 and section 11, the data for the primary endpoint, pathologic response, will be analyzed and reported once all subjects have undergone surgical resection. This will be compared to the historical data that suggest that 10% of sarcoma patients achieve pathologic complete response with neoadjuvant radiation therapy.

<u>Secondary Endpoint</u>
The secondary endpoints overall response rate by RECIST and toxicities will also be analyzed and reported with the initial analysis soon after all patients have completed surgery. Pertinent correlative studies will be reported at this time as well.

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Other secondary endpoints described in section 3 and section 11, overall survival, and time to progression, will be evaluated and reported at 3 and 5 years from the last enrollment.

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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.

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APPENDIX B RECIST GUIDELINES

http://www.eortc.be/recist/documents/RECISTGuidelines.pdf

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APPENDIX C: CTCAE V.4.0

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

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APPENDIX D: CONTRAINDICATIONS AND ADVERSE EVENTS

CONTRAINDICATIONS

Talimogene laherparepvec is contraindicated in patients with a history of life-threatening hypersensitivity to talimogene laherparepvec or any of its excipients.

ADVERSE DRUG REACTIONS

Gastrointestinal disorders SOC:

Very Common (≥ 10%)

- Nausea, Vomiting, Diarrhea, Constipation

Common (≥1% and <10%)

- Weight loss

General disorders and administrative site condition SOC:

Very Common (≥ 10%)

- Chills, Pyrexia, Fatigue, Flu like symptoms, Injection site pain

Common (≥1% and <10%)

- Injection site reactions (including erythema, inflammation, warmth, pain [at injection site and at distant, non-injected lesions], swelling [at injection site and/or lymphadenopathy], or drainage may occur), Malaise

Metabolism and nutrition disorders SOC:

Common (≥1% and <10%)

- Dehydration

Blood and lymphatic system disorders SOC:

Common (≥1% and <10%)

- Anemia

Uncommon (≥0.1% and <1%)

- Plasmacytoma at the injection site

Musculoskeletal and Connective tissue disorders SOC:

Very Common (≥ 10%)

- Myalgia, Arthralgia, Pain in extremity

Infections and Infestations SOC:

Common (≥1% and <10%)

- Cellulitis (see Warnings and Precautions), Oral herpes

Uncommon (≥0.1% and <1%)

- Delayed wound healing

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Injury, poisoning and procedural complications:
Common (≥1% and <10%)
- Bruising

Vascular disorders SOC:
Common (≥1% and <10%)
- Flushing

Nervous System Disorder SOC:
Very Common (≥ 10%)
- Headache

Common (≥1% and <10%)
- Dizziness

Skin and subcutaneous tissue disorders SOC:
Common (≥1% and <10%)
- Vitiligo

Respiratory, thoracic and mediastinal disorders SOC:
Uncommon (≥0.1% and <1%)
- Laryngeal swelling

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
None known.

OVERDOSE
The maximum dose of talimogene laherparepvec that can be safely administered has not been determined.

ABUSE AND DEPENDENCE
Talimogene laherparepvec is not a controlled substance. There is no evidence that talimogene laherparepvec is habit forming or could lead to dependence.

PEDIATRIC USE
No studies of talimogene laherparepvec have been conducted in pediatric subjects.

GERIATRIC USE
There are subjects > 65 as well as > 75 years of age who have received talimogene laherparepvec. However, no adequate and well-controlled studies have been designed to specifically evaluate the use of talimogene laherparepvec in geriatric subjects.

RENAL IMPAIRMENT
No clinical studies have been conducted in patients with severe renal impairment.

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HEPATIC IMPAIRMENT

No clinical studies have been conducted in patients with severe hepatic impairment.

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APPENDIX E: DATA AND SAFETY MONITORING PLAN

In accordance with the NIH policy on procedures for data and safety monitoring of clinical trials, the Holden Comprehensive Cancer Center (HCCC) has developed systems to ensure the safety of participants, the validity and integrity of research data, and compliance with the approved protocol. HCCC Principal Investigators are required to include a general description of a data and safety monitoring plan as part of each new interventional research protocol, which they develop and submit for review.

All investigator-initiated protocols will contain an appropriately detailed Data and Safety Monitoring Plan (DSMP) that will be reviewed and approved by the DSMC or Committee Chair. The DSMC dictates what constitutes a satisfactory plan for each study. All interventional clinical trials require monitoring for data veracity and safety, including physiologic, toxicity- and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III). The method and degree of monitoring needed is related to the degree of risk and should also be commensurate with size and complexity of the trial. The Clinical Research Safety Officer (CRSO) of the DSMC will be the primary interface with the study's PI and research team to collect and assemble all required materials for review by the Committee.

Risk Level

This protocol has been assessed by the Data and Safety Monitoring Committee (DSMC) of the HCCC and by the sponsor-investigator as a **Risk Level 4**. Specifically, a risk-level 4 clinical trial is one that has:

- A risk of death (i.e., 100-day treatment-related mortality) of >5%, or,
- A risk of a Grade 4 SAE (serious adverse event > 15%, or,
- An investigator-sponsored investigational new drug (IND), or,
- Gene therapy, gene manipulation, or viral vector systems, or,
- High-risk clinical procedures performed solely for research purposes, or
- A new chemical or drug for which there is limited or no available safety data in humans

Required DSMP elements

The Principal Investigator for institutional studies at the HCCC must include a trial-specific DSMP with each new protocol. The key items the plan must address are

- A subject eligibility check-list (inclusion / exclusion criteria)
- A list of expected toxicities
- Stopping rules for suspension of accrual secondary to adverse events and safety parameters
- PI's estimate of the study's risk level

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The Principal Investigator is to ensure that all required data for monitoring is provided to the DSMC by way of the CRSO and the HCCC Protocol Manager.

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Eligibility Checklist

Subject ID: _____ Date: _____

Inclusion criteria. All responses must be marked YES or NA for patient to be eligible

1. Subject or subject's legally acceptable representative has provided informed consent. Yes No

2. Histologically confirmed diagnosis of locally advanced STS that is unresectable with clear wide margins, for which preoperative radiotherapy is considered appropriate. Yes No

   EXAMPLES:
   - Resectable stage IIB, III, and IV disease that are not suitable for surgically resection alone due to inability to achieve clear margins.
   - Including metastatic (Stage IV) disease for which radiotherapy and surgical resection are indicated.
   - Except certain histologic subtypes: GIST, Desmoid, Ewing sarcoma, Kaposi sarcoma, and bone sarcomas.

3. Previous treatment: Prior systemic anti-cancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy allowed provided therapy was completed at least one year prior to enrollment. Yes No
   - No prior Talimogene laherparepvec or tumor vaccines allowed.
   - No prior radiation to the same tumor bed allowed.

4. Aged ≥ 18 years Yes No

5. ECOG performance status ≤ 1. Yes No

6. Patient must have measurable disease: Yes No
   - Tumor size at least ≥ 5 cm in the longest diameter as measured by CT scan or MRI for which radiation is feasible.

7. Patient must have injectable disease (direct injection or ultrasound guided). Yes No

Signature: _____ Date: _____

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Eligibility Checklist

Subject ID: _____ Date: _____

Exclusion Criteria. All responses must be marked NO or NA for patient to be eligible

1. Certain histologic subtypes: GIST, Desmoid, Ewing sarcoma, Kaposi sarcoma, bone sarcomas — Yes No
2. History or evidence of sarcoma associated with immunodeficiency states (e.g., Hereditary immune deficiency, HIV, organ transplant or leukemia) — Yes No
3. Subject with retroperitoneal and visceral sarcoma — Yes No
4. History or evidence of gastrointestinal inflammatory bowel disease (ulcerative colitis or Crohn's disease) or other symptomatic autoimmune disease including inflammatory bowel disease or history of any poorly controlled or severe systemic autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus, scleroderma, type I diabetes, autoimmune vasculitis) — Yes No
5. History of other malignancy within the past 3 years except if treated with curative intent and no known active disease present and has not received chemotherapy for ≥ 1 year before enrollment / randomization and low risk for recurrence. — Yes No
6. History of prior or current autoimmune disease. — Yes No
7. History of prior or current splenectomy or splenic irradiation. — Yes No
8. Active herpetic skin lesions. — Yes No
9. Require intermittent or chronic treatment with an anti-herpetic drug (e.g., acyclovir), other than intermittent topical use. — Yes No
10. Any non-oncology vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment and during treatment period. — Yes No
11. Concomitant treatment with therapeutic anticoagulants such as warfarin. — Yes No
12. Known human immunodeficiency virus (HIV) disease (requires a negative test for clinically suspected HIV infection). — Yes No
13. Acute or chronic hepatitis B or hepatitis C infection (requires a negative test for clinically suspected hepatitis B or hepatitis C infection). — Yes No
    - Evidence of hepatitis B
      1. Positive HBV surface antigen (indicative for chronic hepatitis B or recent acute hepatitis B)
      2. Negative HBV surface antigen but positive HBV total core

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antibody (indicative for resolved hepatitis B infection or occult hepatitis B) and detectable copies of HBV DNA by PCR (detectable HBV DNA copies suggest occult hepatitis B).

- Evidence of hepatitis C
  1. Positive HCV antibody and positive HCV RNA by PCR (undetectable RNA copies suggest past and resolved hepatitis C infection).

14. Female subjects who are pregnant or breast-feeding, or planning to become pregnant during study treatment and through 3 months after the last dose of study treatment. Yes No

15. Female subjects of childbearing potential or male subjects unwilling to use 2 highly effective methods of contraception during study treatment and through 3 months after the last dose of study treatment. See section 7.5 for more details. Yes No

16. Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(s). Yes No

17. Other investigational procedures while participating in this study that could affect the primary objective of the study as determined by the PI are excluded. Yes No

18. Previously enrolled in this study. Yes No

19. Receiving any other investigational agents. Yes No

20. Evidence of CNS metastases. Yes No

21. History of allergic reactions attributed to compounds of similar chemical or biologic composition to talimogene laherparepvec. Yes No

22. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness / social situations that would limit compliance with study requirements. Yes No

23. Receiving or requiring immunosuppressive therapies. Yes No

24. Laboratory abnormalities:
    - Hemoglobin < 9.0 g/dL Yes No
    - Absolute neutrophil count (ANC) < 1500 per mm^3 Yes No
    - Platelet count < 100,000 per mm^3 Yes No
    - Total bilirubin > 1.5 X ULN Yes No
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 x ULN Yes No
    - Alkaline phosphatase > 2.5 x ULN Yes No
    - PT (or INR) and PTT (or aPTT) > 1.5 x ULN Yes No
    - Creatinine > 2.0 x ULN Yes No

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Signature: _____ Date: _____

Expected toxicities

The following anticipated risks are identified due to this clinical trial:

- **Very Common side effects** (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** (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 injection 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
  - Areas of skin with loss of color (Vitiligo)
  - 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)

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- **Uncommon side effects** (which may affect between 1 and 10 in every 1000):
  - Injection site reactions: warmth, incision site infection
  - Swelling in the voice box area of your throat that might result in needing 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) in the area where talimogene laherparepvec is injected. Plasmacytoma may be associated with multiple myeloma (a cancer of plasma 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, have had radiation to the site, you should contact the study doctor or his/her study staff immediately.

Other potential side effects

- **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 and sometimes 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 contact the study doctor or his/her study staff immediately. If you have had an allergic reaction to talimogene laherparepvec or any of its ingredients, you should inform your doctor.

- **Autoimmune Reactions:** Autoimmune reactions to the body's own tissues have been reported in some patients administered talimogene laherparepvec. Examples of autoimmune reactions that have been reported in patients receiving talimogene laherparepvec include inflammation of the kidneys (nephritis), blood vessels (vasculitis), lungs (pneumonitis) and worsening psoriasis. It is possible that an autoimmune reaction could occur in any part of the body. Please tell your doctor if you have had any type of autoimmune disease before treatment with talimogene laherparepvec, and all treatments you are receiving for the disease.

Stopping Rules:

As a phase II study, stopping rules do not apply. If a subject dies during active study treatment:

- Trial will be placed on accrual hold until case review
- The death will be reviewed by the principal investigator, IND medical monitor, and IND sponsor (and, as applicable, treating physician)
- Adverse events, including deaths on study, will be reviewed at IND investigators' meeting.

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DSMC Monitoring and Compliance

As a risk level 4 clinical trial, an independent Study Monitor/DSMC, or the DSMC Chair (or his designee), will review study data provided by the PI and the clinical research safety officer (CRSO). The appointed monitor or the DSMC chair (as appropriate) will communicate with the PI at least **quarterly**. Proceedings of the DSMC meeting will be summarized by the CRSO in a brief letter to the PI, a copy of which will be forwarded to the DSMC and PRMC.

To secure protocol compliance and subject safety, the following are implemented:

Accrual:

Subject eligibility will be validated by the DSMC by reviewing the completed eligibility checklist in OnCore prior to the initiation of any study-specific procedures.

Subject accrual data will be entered into the Holden Comprehensive Cancer Center's clinical trials management software OnCore and be available to the clinical research safety officer (CRSO) and the protocol manager.

Adverse events:

Adverse events and serious adverse events will be reported as outlined in protocol Section 7: Adverse Events: List and Reporting Requirements. The principal investigator or designee will report adverse events to the DSMC via OnCore as outlined in protocol Section 7.7: Expedited Adverse Event Reporting. The principal investigator or designee will report serious adverse events to the DSMC via OnCore as outlined in protocol Section 7.7.3: Reporting Procedures for Serious Adverse Events.

Audits:

Audits will be done at least **quarterly** and performed by the CRSO or designee. Audit reports will be provided to the study monitor (if appointed) and the DSMC chair for review and discussion with the study PI. Final audit reports are sent to the DSMC, the PRMC chair, the PI, the protocol manager, and the Human Subjects Office / IRB.

At minimum, audits will:

- validate eligibility of patients enrolled to the study
- verify a signed informed consent document
- determine protocol compliance
- determine if SAEs were reported to appropriate internal and external regulatory agencies
- compare veracity of data in research records with source documents
- review investigational drug processing and documentation
- assess cumulative AE and SAE reports for trends and compare to study stopping rules

Annual report

The principal investigator will provide an annual progress report to the DSMC and PRMC *via* the protocol manager. At minimum, the annual progress report will provide the

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following:

- Current trial status with a summary of study progress to date, including accrual difficulties or successes, modifications or amendments, brief overview of toxicities, AE and SAE, and unexpected findings or events.

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