Phase II multicenter study of talimogene laherparepvec in classic or endemic Kaposi sarcoma
KAPVEC

INTERVENTIONAL RESEARCH PROTOCOL
RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

Version N°3.0 of 16/10/2020
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INTERVENTIONAL RESEARCH PROTOCOL

PROTOCOL SIGNATURE PAGE

Research code number: APHP190871

Title: Phase II multicenter study of talimogene laherparepvec in classic or endemic Kaposi sarcoma
KAPVEC Study

Version N° 3.0 of 16/10/2020

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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1 SUMMARY

Full title	Phase II multicenter study of talimogene laherparepvec in classic or endemic Kaposi sarcoma
Acronym	KAPVEC
Coordinating Investigator	Pr Céleste LEBBE Oncodermatologie - Hopital Saint Louis
Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	Kaposi sarcoma (KS) is a lymphangioproliferation associated with human herpes virus 8 (HHV8) promoted by immunosuppression. HIV-related KS and iatrogenic posttransplantation KS are treated by immune restoration, in association with local or systemic therapies as chemotherapies if required. Conversely in classic and endemic KS, the underlying relative immunosuppression cannot be directly targeted. Treatment is poorly codified, mostly based on surgery or radiotherapy for localized KS. Most aggressive forms with visceral involvement are treated with chemotherapies or interferon, which give at best 30-60% of transient responses and may not be well tolerated in elderly patients. Talimogene laherparepvec is the first oncolytic immunotherapy approved by the FDA, in metastatic or unresectable melanoma with injectable nodal or cutaneous lesions. It is designed to induce tumor regression of injected lesions through direct lytic effects, and of uninjected lesions through induction of systemic antitumor immunity. In Merkel cell carcinoma (MCC), another virus-induced tumor, treatment with PD-1/PD-L1 axis inhibitors have proven efficacy, thus providing a proof of principle that immunotherapy could be effective in virus-induced tumors. Two cases of metastatic MCC succesfully treated with talimogene laherparepvec were recently reported, suggesting that talimogene laherparepvec may also be an effective therapeutic option. Considering the high immunogenicity of viral epitopes in KS tumors, the role of the immune evasion in the development of KS, and the cutaneous manifestations (>90% of patients) that can be easily injected, classic and endemic KS is a good tumor model to be targeted with talimogene laherparepvec.
Main objective and primary endpoint	The main objective is to assess whether talimogene laherparepvec is clinically inactive (partial+complete response probability $\pi 0<10\%$) or truly active (partial+complete response probability $\pi 1>40\%$) in classic and endemic Kaposi sarcoma. The primary endpoint is the best overall response rate (BORR) defined by the occurrence of complete response or partial response of the injected lesions following PGA criteria (PGA 0 to 4) recorded from the start of treatment

	until 6 months or the beginning of any other specific therapy for Kaposi sarcoma if it occurs before 6 months.
Secondary objectives and endpoints	Secondary objectives: - Safety profile of talimogene laherparepvec in classic and endemic Kaposi sarcoma - Other parameters of efficacy (best response, response rate, duration of response) - Efficacy on injected and uninjected lesions - Quality of life Exploratory objectives - To characterize the efficacy of talimogene laherparepvec related to immunologic and viral assessment on tumor biopsies and blood samples Secondary endpoints: - Adverse events (following the CTCAE v5.0) - BORR according to the ACTG criteria, response rate at month 3 and 6, response rate on lymphedema, time to response, duration of response - Response on injected and uninjected target lesions - Deaths from any cause - KS-adapted DLQI score Exploratory endpoints: - Characterize the immune tumor infiltrate (immune cells quantification), viral infiltrate and tumor necrosis before and after treatment - HHV8 viral load in blood and tumor cells; HHV8 sequencing
Design of the trial	Phase II multicentre single arm open label trial
Population of trial subjects	Adult patients
Inclusion criteria	- Classic or endemic histologically confirmed Kaposi sarcoma (KS) that is progressive, but does not require a systemic therapy ; - Injectable and measurable disease, defined as: • At least 2 cutaneous lesion ≥10mm in its largest diameter, in a not previously irradiated field; • At least 2 other cutaneous lesion ≥10mm in their largest diameter available for repeated cutaneous biopsies, in a not previously irradiated field. NB: Each cutaneous lesion can be replaced by a cluster of small lesions with edge to edge distance <2 mm, if the biggest diameter of each cluster meet the previous criteria. - Be willing to provide tissue from cutaneous biopsy; - At least 4 weeks washout for all KS specific therapies including topical treatment, chemotherapy, radiotherapy and immunotherapy including interferon; - Provide written, informed consent prior to the performance of any study specific procedures;

	- Be more than 18 years of age on day of signing informed consent. - Have a performance status of 0 or 1 on the ECOG Performance Scale. - Demonstrate adequate organ function: Haematological : Absolute neutrophil count (ANC) ≥1500/mm^3; Platelets ≥100 000/mm^3; haemoglobin≥ 8 g/dL; Renal: Serum creatinine ≤ 1.5 x upper limit of normal (ULN), OR calculated creatinine clearance ≥ 40mL/min (using MDRD formula) for subject with creatinine levels > 1.5 x ULN. Hepatic: AST (SGOT) and ALT (SGPT) ≤ 2.5xULN, serum total bilirubin ≤ 1.5xULN OR direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5xULN. PT≤1.5; PTT (TCA) ≤1.5 - Female subject of childbearing potential should have a negative serum pregnancy within 72 hours prior to receiving the first dose of study medication - Have a health insurance.
Exclusion criteria	- Known history of organ transplantation, including allogeneic stem-cell transplantation, or HIV (HIV 1/2 antibodies detected at selection); - Symptomatic visceral involvement of KS including brain metastases; - Active autoimmune disease that requires systemic treatment or has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Patients with vitiligo, type I diabetes mellitus, hypothyroidism, psoriasis non requiring systemic treatment are permitted to enrol; - Evidence of clinically significant immunosuppression such as the following: primary immunodeficiency state such as Severe Combined Immunodeficiency Disease; concurrent opportunistic infection; - Receiving systemic immunosuppressive therapy including oral steroid doses > 10 mg/day of prednisone or equivalent within 7 days prior to enrolment; - Clinically significant cardiac dysfunction (symptomatic heart failure, clinically significant arrhythmia or conduction disorders); - Active herpetic skin lesions or prior complications of HSV-1 infection (eg, herpetic keratitis or encephalitis);

	- Intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use; - Previous treatment with talimogene laherparepvec or any other oncolytic virus; - Prior radiotherapy in which the fields overlap the injection sites; - Prior immunosuppressive, chemotherapy, radiotherapy, biological cancer therapy, or major surgery within 28 days prior to enrollment or has not recovered to CTCAE grade 1 or better from adverse event due to KS therapy administered more than 28 days prior to enrollment. - Prior therapy with tumor vaccine; - Received live vaccine within 28 days prior to enrolment; - Currently treatment with another investigational device or drug study, or less than 28 days since ending treatment with another investigational device or drug study(s); - Acute or chronic active hepatitis B (HbS Ag detected) or C infection (HCV RNA detected) at inclusion; or active TB (Bacillus Tuberculosis). - Known additional malignancy that is currently progressing or requires active treatment within the last 3 years. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer; - Sensitivity to any of the products or components to be administered ; - Psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial; - Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial and 3 months after the last dose of talimogene laherparepvec; - Subjects who are unwilling to minimize exposure with his/her blood or other body fluids to individuals who are at higher risks for HSV-1 induced complications such as immunosuppressed individuals, individuals known to have HIV infection, pregnant women, or infants under the age of 3 months, during talimogene laherparepvec treatment and through 30 days after the last dose of talimogene laherparepvec. - Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial. - Female subject of childbearing potential who are unwilling to use acceptable method(s) of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec.

	- Sexually active subjects and their partners unwilling to use male or female latex condom to avoid potential viral transmission during sexual contact while on treatment and within 30 days after treatment with talimogene laherparepvec. In addition, male participants should not donate sperm from 3 months after last dose. - Vulnerable subjects: prisoners incarcerated following administrative or court decision, subjects with psychiatric disorders who are involuntary hospitalized, subjects under legal protection measure, subjects who cannot express their consent.
Investigational medicinal product(s)	Talimogene laherparepvec Dose: 10^6 pfu/ml at week 1 then 10^8/ml at week 4 and every 2 weeks (up to 4ml for each injection) Route: intralesional injection Duration of treatment: 6 months (12 cycles)
Comparator treatment	-
Interventions added for the trial	Immunovirologic evaluations based on tumor tissue collection (cutaneous biopsy) and correlative blood sampling
Risks added by the trial	Risk D
Scope of the trial	Kaposi sarcoma
Number of subjects included	9 patients will be enrolled in the first part of the study with another 11 patients in the second part (total 20 patients). It implies to screen a maximum of 40 patients.
Number of sites	National multicenter study: 2 sites
Duration of the trial	Inclusion period: 18 months Participation period (treatment+follow-up): 1 month of screening + 12 cycles (≈6 months) of treatment + 1 month of follow up Total duration: 26 months
Number of enrolments expected per site and per month	Saint-Louis: 0-2 Cochin: 0-1
Statistical analysis	Simon's 2 stage Optimal Design Interim analysis planned after 9 patients
Sources of funding for the trial	Amgen
Trial will have a Data Monitoring Committee	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE TRIAL

2.1 Hypothesis for the study

Oncolytic viruses represent a novel drug class in which native or modified viruses are used for the treatment of cancer. Oncolytic viruses mediate tumor regression through a virus-induced lytic effect in tumor cells, and through the activation of the innate immune system by the virus coupled with antigen release by dying tumor cells. It creates a favorable microenvironment for the adaptive systemic antitumor immunity, thus being able of regressing tumor at distant, uninjected sites.

Talimogene laherparepvec is an attenuated herpes simplex virus type 1 (HSV-1) derived by functional deletion of 2 genes, ICP34.5 and ICP47, and insertion of coding sequence for human granulocyte macrophage colony stimulating factor (GM-CSF). Deletion of ICP34.5 allows selective replication of talimogene laherparepvec in tumor tissue; normal cells are able to protect against talimogene laherparepvec infection as they contain intact anti-viral defense mechanisms. Deletion of ICP47 prevents down-regulation of antigen presentation molecules and increases the expression of HSV US11 gene, which enhances viral replication in tumor cells. GM-CSF recruits and activates antigen presenting cells which can process and present tumor-derived antigens to promote an effector T-cell response (1).

In virus-induced tumors as Kaposi sarcoma, there is a growing evidence that immunotherapy could be more effective than the usual treatments as chemotherapy. In Merkel cell carcinoma (MCC), another virus-induced tumor, treatment with immune checkpoint inhibitors as PD-1/PD-L1 axis inhibitors have proven efficacy in phase II trials (2,3). Two cases of metastatic MCC successfully treated with talimogene laherparepvec were recently reported, suggesting that talimogene laherparepvec may also be an effective therapeutic option (4). In KS, our team and others reported some cases of patients successfully treated with PD1 blockade (5,6); some clinical studies are currently ongoing. Considering the high immunogenicity of viral epitopes in KS tumors, the role of the immune evasion in the development of KS, and the cutaneous manifestations (>90% of patients) that can be easily injected, classic and endemic KS appears as a good tumor model to be targeted with talimogene laherparepvec.

2.2 Existing knowledge relating to the condition under investigation

Kaposi's sarcoma (KS) is characterized by a multifocal proliferation of lymphatic endothelium-derived spindle cells infected with an oncogenic virus, herpesvirus-8 (HHV-8) (7–9). Two major settings of KS should be distinguished from a clinical point of view: KS occurring in the context of immunosuppression, that are HIV-associated KS and post-organ transplant KS, and classic and endemic KS. Classic and endemic KS occurs in patients from the Mediterranean area or Africa, outside of any established immunosuppression apart from immunosenescence and immunoevasion directly linked to HHV-8 infection (10,11).

KS treatment depends on the KS type, the extent of the disease, the disease course and on patient’s symptoms. The treatment of HIV associated or post-organ transplant KS relies on immune restoration with the help of anti-retroviral drugs for HIV patients, and gradual minimization of immunosuppressive therapy +/- mTOR introduction for post-transplant KS, eventually associated with temporary chemotherapy (12). By contrast, systemic treatment of classic KS remains poorly codified since immunosenescence and HHV-8 induced immunoevasion are not yet amenable to specific management. This lymphangioproliferation

usually occurs in elderly patients (mean age 68 years) and has a chronic evolution. It is generally indolent, with localized cutaneous lesions managed either by simple monitoring or local treatment. There is no randomized clinical trial comparing these different local treatment modalities. Radiotherapy is one of the most efficient local treatments of KS. Overall response rates varied from 40% to 90%, while surgical excision is grieved with a high recurrence rate. The administration of intralesional chemotherapies have been tested with good response rates for example, 70% with vinblastine. Topical treatments as imiquimod and alitretinoin gel has shown some efficacy with respectively 50% and 37% of response (Pages et al, 2018).

Conversely, in classic KS, symptomatic visceral lesions requiring systemic treatments are exception. In our experience around 20% of patients will experience progressive cutaneous extension with an increased number of skin lesions occasionally ulcerated and painful, and/or with the appearance of disabling lymphedema. These more aggressive forms require systemic therapy. The treatment is then poorly codified. It is generally based on low myeloablative chemotherapies (bleomycin, etoposide, vinblastine) and more recently, based on the experience gained on HIV associated KS, on the use of liposomal anthracyclines and weekly taxanes, with an objective response rate (mainly partial responses) ranging from 30 to 60% often unsustainable (13). Interferon alpha at small doses is effective in our experience in about 60% cases (prolonged partial responses), but this drug is often poorly tolerated in elderly patients (12). Recently PD1 blockade was reported to be a very promising treatment in advanced KS, inducing sustained complete response in severe endemic KS (5,6).

2.3 Summary of relevant pre-clinical and clinical trials

Preclinical studies demonstrated that talimogene laherparepvec demonstrated strong lytic activity against a variety of human tumor cell lines in vitro, including colorectal cancer, breast cancer, glioblastoma, astrocytoma, prostate adenocarcinoma and melanoma (1). Murine models demonstrated tumor infiltration by CD8+ T-cells in both injected and noninjected metastases. Melanoma patients treated with talimogene laherparepvec demonstrated accumulation of melanoma antigen specific CD8+ T-cells within injected lesions associated with a reduction in CD4+ FoxP3+ regulatory T-cells and CD14+ myeloid-derived suppressor cells (14). Collectively, these observations demonstrate the ability of talimogene laherparepvec to lyse human tumor cells, and induce antigen-specific CD8+ adaptive immune responses in both injected and uninjected tumors.

Talimogene laherparepvec was studied in melanoma. A phase III study injectable melanoma patients treated with intralesional talimogene laherparepvec or subcutaneous GM-CSF showed an ORR of 26.4% vs 5.7%, and an overall survival of 23.3 vs 18.9 months (15). Talimogene laherparepvec is the first approved oncolytic virus.

Overall, most adverse events reported in patients treated with talimogene laherparepvec included flu-like symptoms and injection site reactions. No fatal adverse events related to talimogene laherparepvec were reported.

2.4 Description of the population of trial subjects and justification for the choice of subjects

Endemic and classic KS are observed in elderly patients; the evolution is more often indolent, with limited cutaneous involvement. Nevertheless in some patients extensive cutaneous and visceral manifestations are observed leading to systemic chemotherapy, and more recently to treatment with PD1 inhibitor. To date, while PD1 inhibitors are actively developed in advanced

KS, no immunomodulatory agents are used in cutaneous KS beyond interferon, which is not well tolerated in elderly patients. Classic/endemic KS represents an ideal model for evaluating new drugs since patients do not receive concomitant immunosuppressive regimens nor antiviral therapies (in opposition to HIV or post-organ-transplant KS) (13). Moreover most patients had cutaneous lesions that are easily accessible to a local or intralesional treatment.

2.5 Name and description of the investigational medicinal product

Talimogene laherparepvec (Imlygic) is an oncolytic immunotherapy based on a modified herpes simplex virus type 1 (HSV-1), delivered by intralesional administration.

2.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

Talimogene laherparepvec will be given by intralesionnal injection at the dose of 10^6 pfu/ml (up to 4 ml) at week 1, then 10^8 pfu/ml (up to 4 ml) at week 4 and every 2 weeks, only in KS cutaneous lesions, up to 6 months or complete regression of injected lesions, clinically significant progression or unacceptable toxicity.
See Section 7 for further information about the administration of the product.

2.7 Summary of the known and foreseeable benefits and risks for the study participants

The study will provide an overview of efficacy and safety of talimogene laherparepvec in classic and endemic KS. The benefit risk ratio seems favourable since talimogene laherparepvec has previously been tested in several phase 2 and 3 studies in other diseases as melanoma and showed an acceptable safety profile, while the only immunomodulator agent approved in KS (interferon) is poorly tolerated.
If it has some positive effects, the benefit of the drug will be further evaluated on larger series.
A more detailed description of the risks imposed by the research is included in the "Safety Assessment" section.

3 OBJECTIVES

3.1 Primary objective

The main objective is to assess whether talimogene laherparepvec is clinically inactive (partial+complete response probability π0<10%) or truly active (partial+complete response probability π1>40%) in classic and endemic Kaposi sarcoma.

3.2 Secondary objectives

Secondary objectives are:
- to assess the safety profile of talimogene laherparepvec in classic and endemic Kaposi sarcoma;
- to assess other parameters of efficacy, on injected and uninjected lesions (best response, response rate, duration of response);
- to assess the disease-related quality of life during treatment.

3.3 Exploratory objectives

Collateral research will be performed to characterize the efficacy of talimogene laherparepvec related to immunologic and virologic assessment and on tumor biopsies and blood samples in order to:
- Characterize the immune tumor infiltrate (immune cells quantification), viral infiltrate and tumor necrosis before and after treatment;
- During treatment, the HHV8 viral load will be monitored in blood and tumor cells, HHV8 will be sequenced and HSV1 will be quantified.

4 DESCRIPTION OF THE TRIAL

4.1 Concise description of the primary and secondary endpoints

4.1.1 Primary endpoint

The primary endpoint is the best overall response rate (BORR) defined by the occurrence of complete response or partial response of the injected lesions following PGA criteria (PGA 0 to 4) recorded from the start of treatment until 6 months or the beginning of any other specific therapy for Kaposi sarcoma if it occurs before 6 months.

4.1.2 Secondary endpoints

Secondary endpoints are:

1/ Safety endpoints
- Safety will be assessed in terms of drug toxicity evaluated by clinic and changes in laboratory parameters, and scored according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

2/ Efficacy endpoints
- the best overall response rate (BORR) of the injected and uninjected target lesions according to the ACTG criteria,

- the best overall response rate (BORR) of the uninjected target lesions according to the PGA criteria,
- the response rate of the injected and uninjected target lesions at month 3 and month 6 according to the PGA and ACTG criteria,
- the response rate on lymphedema at month 3, month 6 and at best response (as defined by the primary endpoint),
- the time to response, defined as the time to first response (PGA criteria) recorded from the start of treatment,
- the duration of response, defined as the time from first response (PGA criteria) to progression,
- Deaths from any cause;
- KS-adapted DLQI (dermatology life quality index)

4.1.3 Exploratory endpoints

The immunological sub-study will include:
- Characterization of the tumor microenvironnement by immunohistochemistry: immune cells infiltration (quantification of CD3, CD4, CD8, FoxP3+ T cells);
- Analysis of the immunomodulation induced by the treatment on peripheral blood: T cells (CD4, CD8, anti-HHV-8 T cells).

Virological analyses:
- The HHV8 viral load will be quantified in blood and tumor sample using quantitative real time PCR.
- Quantification of HSV-1 DNA and specific PCR for T-VEC
- HHV8 sequencing

At baseline and during treatment (cycle 3/week 6).

4.2 Research methodology

4.2.1 Design of the trial

Multicenter single arm open-label phase II study. The design of this phase II trial is an optimum Simon's two-stage design to test the null hypothesis that the best overall response rate (BORR) of CR or PR (PGA 0 to 4), $P \leq 0{,}100$ versus the alternative that $P \geq 0{,}400$. This a two stage design; after testing the drug on 9 patients in the first stage, the trial will be terminated if 1 or fewer respond and will continue if 2 or more patients respond. If the trial goes on to the second stage, a total of 20 patients will be studied. If the total number responding is less than or equal to 4, the drug is rejected.
Between the 2 stages, inclusions could be suspended until the observation of the BORR at 6 months of the last included patient of the first stage. Nevertheless, if 2 CR or PR are observed before patient 9, no stopping in the inclusions is required.

4.2.2 Number of participating sites

This is a multicenter French national study including 2 participating centres, members of the Groupe de Cancérologie Cutanée.
Patients will be recruited in hospital by dermatologist experts in KS management.

4.2.3 Identification of the subjects

The subjects participating in this study will be identified as follows:
Site number (3 digits) - Sequential selection number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the trial.

5 PROCEDURE FOR THE TRIAL

Before any examination or intervention may be carried out for the trial, the investigator must obtain the *free, informed and written consent of the subject participating in the trial, or of his/her legal representative* where applicable.

Subjects participating in the clinical studies described in article L.1121-1(1° paragraph) of the Code de la Santé Publique are eligible for prior medical examination appropriate for the trial.

The screening, follow-up and end-of-study visits can be performed at a out-patient basis or in hospitalisation upon investigator choice.
They will be performed by the investigator or his/her qualified designee.

5.1 Screening and inclusion visit

The screening visit takes place between 5 days and 1 month (30 days) before the baseline/W1 visit.

Whose consent must be obtained	Who informs the individual and collects their consent	When is the individual informed	When is the individual's consent collected
The subject participating in the trial	The investigator (usually a dermatologist or oncologist) or his qualified designee	At the selection visit	After a delay of reflexion of at least 24 hours

For collection of subject's consent, see Chapter 14.1. Once a patient is selected and consent is signed, a "Patient Selection Form" will be sent to SBIM (Service de biostatistique et informatique médicale). The allocation of identification number will be handled by the statistical data centre (this identification number will be retained for the entire research).

Medical history and medications
The investigator or qualified designee will review a medical history including active or recent conditions that are considered to be clinically significant, prior medication taken by the subject within 28 days before starting the trial, and concomitant medications.

Disease details
The investigator or qualified designee will obtain prior and current details regarding KS status: date of diagnosis, date and results of the cutaneous biopsy that confirmed the

diagnosis, disease stage and all prior KS treatments including surgeries, radiation, local and systemic treatments.

Clinical assessments
· Height, weight and ECOG Performance Status will be checked.
· A complete physical examination will be performed and will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, peripheral vascular system and neurologic system. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Laboratory tests
Following blood samples will be assessed:

- Blood samples:

Haematology: WBC count plus differential (total neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil and other counts), RBC count, haemoglobin, haematocrit and platelet count
Clinical chemistry: Sodium, potassium, chloride, bicarbonate, total calcium, inorganic phosphate, magnesium, urea, creatinine, creatinine clearance, glycemia, bilirubin (total, indirect and direct), AST, ALT, alkaline phosphatase, gamma-glutamyl transferase, albumin.

All patients will have a serology HIV (HIV1/2 antibodies), and the determination of HSV1 status at baseline (HSV1 antibodies). All females of childbearing potential will have a serum pregnancy test.

- Urinary samples: blood, glucose, protein (urine test strip)

Patient will be evaluated against study inclusion and non-inclusion criteria. When the patient is considered eligible to be included in the study the Investigator will complete the “Patient Inclusion Form” and send it to SBIM.

5.2 Baseline/W1 visit

After the verification of inclusion and exclusion criteria, the following data will be collected.

Clinical assessments
· Weight
. ECOG Performance Scale
. Echelle numerique (pain numeric scale)
. KS-adapted DLQI score
. A complete physical examination similar to screening/inclusion visit.
· Assessment of the disease including the definition of target lesions as described in Section 8.2 and 18.5.
· Colour photography: total-body photographs, as well as detailed photographs of target lesions (injected and uninjected lesions) and their identification, and any other notable features of the patient's KS.

Laboratory procedures will be performed locally prior to injection if they have been made over 1 week. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to injection.

- Blood samples:

Haematology: WBC count plus differential (total neutrophil, lymphocyte, monocyte, eosinophil, basophil counts), RBC count, haemoglobin, haematocrit and platelet count; PT;TCK
Clinical chemistry: Sodium, potassium, chloride, bicarbonate, total calcium, inorganic phosphate, magnesium, urea, creatinine, creatinine clearance, glycemia, bilirubin (total, indirect and direct), AST, ALT, alkaline phosphatase, GGT, albumin.

- Urinary samples: blood, glucose, protein (urine test strip)

All females of childbearing potential will have a urine pregnancy test. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-HCG is performed and found to be negative. If positive, the patient must be discontinued from the study.

Immunologic and virologic assessment
A blood sample and a cutaneous biopsy of a Kaposi lesion will be realized (see Section 8.3.1 for detailed procedure).

Injection
Clinical assessment, laboratory procedures and cutaneous and blood sampling must be performed before the first intralesional injection.
A premedication with paracetamol 1g at least 1h before the 1st injection may be administered upon investigator choice to prevent injection reaction.
The injection site may be treated with a topical anaesthetic agent upon investigator choice (ex: topical lidocaine or injectable xylocaine). Injectable anaesthetic may be injected around the periphery of the lesion but should not be injected directly into the lesion (see 18.6 for detailed procedures).

Monitoring of adverse events
The investigator or qualified designee will assess the occurrence of a potential AE after the injections. AEs will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE v5.0.

Toxicities will be characterized in terms of seriousness, causality, toxicity grading, and action taken with regard to trial treatment (refer to section 10).

5.3 Treatment visits

Follow-up visits are planned at W4 then every 2 weeks on the day of each injection with talimogene laherparepvec.
Patients will be evaluated at each visit for safety, and up to 1 month after the last injection.
Clinical response will be assessed every 2 cycles (once a month) and until the end-of-study visit.

Talimogene laherparepvec should be administered after all assessments have been completed. A premedication with paracetamol 1g at least 1h before each injection may be administered upon investigator choice to prevent injection reaction.
The injection site may be treated with a topical anaesthetic agent upon investigator choice (ex: topical lidocaine or injectable xylocaine). Injectable anaesthetic may be injected around the periphery of the lesion but should not be injected directly into the lesion (see 18.6 for detailed procedures).

Treatment may be administered up to 1 day before / 3 days after the scheduled day due to administrative reasons. Administration out of this window must be reported as a protocol deviation.

Clinical assessments
Clinical data are listed below:
· Weight
. ECOG Performance Scale
. Echelle numerique (pain numeric scale)
. KS-adapted DLQI (at cycle2/W4D1 and every 2 visits (once a month)
. Vital signs
. Physical examination similar to W1 visit
. Target lesions (injected and uninjected lesions) will be measured every 2 visits (once a month) (refer to section 8.2 and 18.5).
. Interview of patient regarding the risk of herpetic infections in its relatives (refer to section 18.7)
· Colour photography: total-body photographs, as well as detailed photographs of target lesions (injected and uninjected lesions) and any other notable features of the patient's KS, will be taken every 2 visits (once a month).

Monitoring of adverse events
The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs. AEs will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE v5.0.

Toxicities will be characterized in terms of seriousness, causality, toxicity grading, and action taken with regard to trial treatment (refer to section 10).

Laboratory procedures will be performed on sites and can be conducted up to 72 hours prior to injection. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each injection.

- Blood samples

Haematology: WBC count plus differential (total neutrophil, lymphocyte, monocyte, eosinophil, basophil counts), RBC count, haemoglobin, haematocrit and platelet count; PT; TCK
Clinical chemistry: Sodium, potassium, chloride, bicarbonate, total calcium, inorganic phosphate, magnesium, urea, creatinine, creatinine clearance, glycemia, bilirubin (total, indirect and direct), AST, ALT, alkaline phosphatase, GGT, albumin.

- Urinary samples: blood, glucose, protein (urine test strip)

All females of childbearing potential will have a urine pregnancy test. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-HCG is performed and found to be negative. If positive, the patient must be discontinued from the study.

Immunologic and viral assessment
A blood sample and a biopsy of an injected and an uninjected KS cutaneous lesion will be realized at week 6 (see Section 8.3.1 for detailed procedure). It must be taken prior to the injection of talimogene laherparepvec that is planned the same day (cycle 3, W6D1).

5.4 End of study visit

- In case of planned end of treatment after 12 cycles of treatment: the end-of-study visit takes place 4 weeks after last trial drug administration.
- In case of premature termination (refer to 5.9.1):

- For progression: the end-of-study visit takes place 4 weeks after the last trial drug administration.
- For other cases of premature termination: the end-of-study visit takes place 4 weeks after the last trial drug administration, and response to treatment will be registered up to 6 months from baseline. After premature cessation of treatment, every effort will be made to collect information regarding disease status until the start of new specific therapy for KS, disease progression or death.

The investigations scheduled for the end-of-study visit are:

Clinical assessments – idem 5.3 Treatment visit, including the KS-adapted DLQI.

Monitoring of adverse events – idem 5.3 Treatment visit

Laboratory procedures – idem 5.3 Treatment visit

Immunologic assessment
A blood sample will be taken at the EOT visit (see Section 8.3.1 for detailed procedure).

5.5 Expected length of participation, chronology and duration of the study.

	Month
Maximum period between screening and enrolment	1
Length of Inclusion period	18
Duration of participation for each subject, of which:	
• Treatment period:	12 cycles (≈6 months)
• Follow-up period:	1
Total study duration:	26

5.6 Table or diagram summarising the chronology of the study

Actions		D-30 days Selection and Inclusion	Cycle 1 W1D1 Baseline	Cycle 2 W4D1 (-1/+3 days)	Cycle 3 W6D1 (-1/+3 days)	Cycle 4 to 12 W8D1 à W24D1 (-1/+3 days)	EOS (W28 or early termination) (-1/+3 days)
Information		X					
Signature of the consent form		X					
Past medical history and KS history		X					
Physical exam	Visit	X	X	X	X	X	X
	Vital signs	X	X	X	X	X	X
	Assessment of AE		X	X	X	X	X
	Photography		X	X		X/4wks	X
	KS-adapted DLQI		X	X		X/4 wks	X
Standard assessment	Biology*	X	X	X	X	X	X
	Pregnancy test (serum or urinary)	S	U	U	U	U	U
Pharmaco – Dynamics**	Blood sample		X		X		X
	Cutaneous biopsy		X		X		
Dispensation of treatments			X	X	X	X	

Table 1: Flow Chart

AE, adverse events; EOS: end of study.

* Biological testing performed at selection/inclusion and before each cycle will include:
- Blood samples: haematology (WBC count plus differential, RBC count, haemoglobin, haematocrit and platelet count), clinical chemistry (sodium, potassium, chloride, bicarbonate, total calcium, inorganic phosphate, magnesium, urea or blood urea nitrogen (BUN), creatinine, creatinine clearance, glycemia, bilirubin (total, indirect and direct), AST, ALT, alkaline phosphatase, albumin; PT, TCK
- Urine samples: blood, protein glucose (urine test strip), and urine pregnancy test for women with childbearing potential.
An additional blood testing including HIV1/2 antibodies detection, HSV1 status and a serum pregnancy test will be added at selection.

** For immunovirologic analyses, blood samples and cutaneous biopsies will be collected (before injection) (see Section 8.3.1 for detailed procedure).

5.7 Distinction between standard care and research

TABLE: "Standard care" vs. "added interventions" required specifically for the study

Procedures and treatments to be provided during the study	Procedures and treatments associated with <u>standard care</u>	Procedures and treatments added for the <u>study</u>
Treatments		Injection of talimogene laherparepvec Premedication with paracetamol 1g 1h before each injection

		Topical anaesthetic agent (ex: topical lidocaine or injectable xylocaine) before each injection
Consultations	Visit twice a month during the treatment phase	
Blood samples	Standard blood analyses twice a month during treatment phase	HIV test at baseline HSV1 status at baseline Pregnancy test before each injection Collection of blood samples at baseline , at W6 and EOS
Imaging, etc.	Photography	Cutaneous biopsy at baseline and at W6

5.8 Biological samples

The samples that are taken during the trial will be stored in a biological sample bank.

A biological collection from samples collected before the first dose of study drug, after 2 cycles (at W6) will be made for all patients.

Immunovirologic studies will be done:

- in the Pathology Department, AP-HP Hôpital Saint-Louis, Paris, supervised by Dr BATTISTELLA for immuhistochemical analysis.

- in the Virology Department, AP-HP Hôpital Saint Louis, Paris for virological studies under the supervision of Pr LE GOFF.

- in the Immunoly Department, AP-HP Hôpital Robert Debré, Paris, for blood samples (Pr CARCELAIN).

At the end of the trial, the samples that will not have been used for immunovirologic studies will be stored for 15 years. Their use for further analysis not described in the initial protocol will be submitted to the approval of a new protocol (by the legal authorities and Amgen) and only if the subject is informed and gives additional consent, as stated in the information sheet/consent form.

Type of sample	**Quantity**	**Storage location**	**Manager of the sample bank**	**Purpose of the sample bank**	**Storage period**	**Outcome (destruction, etc.)**
Blood	2 tubes (baseline, week 6, EOT)	Pharmacology - AP-HP Hopital Saint Louis	Pr MOURAH	Further immunologic analyses	15 years	Research Destruction after 15 years
Tumor samples	2 blocks (baseline, week 6)	Pathology AP-HP Hopital Saint Louis	Dr BATTISTELLA	Further tumor analyses	15 years	Research Destruction after 15 years

In the event of Amgen declining support of a future protocol involving those stored samples, the samples be destroyed.

5.9 Termination and exit rules

5.9.1 Criteria and procedures for terminating the study treatment

Different situations

- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the subject's source file and the case report form (CRF);
- Premature termination of treatment, but the subject remains enrolled in the study until the end of the subject's participation: the investigator must document the reason;
- Premature termination of treatment and exit from the study;
- Planned termination of the study.

5.9.1.1 Temporary interruption of the study treatment

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events). Subjects should be placed back on study therapy within 4 weeks of the scheduled interruption (ie, approximately 6 weeks from the previous dose), unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.9.1.2 Permanent premature termination of the study treatment

A subject must be discontinued the treatment before the planned termination after 12 cycles, for any of the following reasons:

- In case of progression, treatment could be continued to allow delayed response after consultation with the principal investigator of the centre and the investigator coordinator, and patient information.
- Unacceptable adverse events that is considered related to talimogene laherparepvec as described in Section 10;
- If talimogene laherparepvec dosing is delayed by more than 8 weeks from the date of the planned dose due to the occurrence of an adverse event that is considered related to talimogene laherparepvec, the subject must be permanently withdrawn from study treatment;
- The subject withdraws consent;
- The subject, for any reason, requires treatment with another therapeutic agent for treatment of the study disease. In this case, discontinuation from the treatment occurs immediately upon introduction of the new agent;
- Intercurrent illness that prevents further administration of treatment;
- Investigator’s decision to withdraw the subject: the investigator can permanently withdraw a subject from the study for any safety reason, or if it is in the subject's best interest;
- A female subject becomes pregnant or fails to use acceptable method(s) of effective contraception (for those subjects who are able to conceive); a female subject breast feeds while on study treatment;
- The subject is lost to follow-up: the subject cannot be located. The investigator must make every effort to reconnect with the subject (and record his attempts in the source file), at least to determine whether the subject is alive or dead.

Subjects may exit the study at any time and for any reason.

5.9.1.3 Planned termination of study treatment

A subject completed 12 cycles of uninterrupted treatment with talimogene laherparepvec, or complete response of KS injected lesions if it occurs before cycle 12.

5.9.1.4 Criteria and procedure for premature withdrawals and exits from the study

If a subject exits the trial prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

The case report form must list the various reasons why the subject exited or was withdrawn from the study:

- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Other medical problem
- ☐ Subject's personal reasons
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up
- ☐ Other

5.9.2 Monitoring subjects after the premature termination of treatment

The end-of-study visit takes place 4 weeks after the last trial drug administration, in case of planned end-of-treatment after 12 cycles or premature termination (post treatment follow-up period). The investigations scheduled for the end-of-study visit are defined in Section 5.4. The appropriate case Report Form (CRF) section must be completed.

After premature termination of treatment, the investigator must:

- Document the reason(s) ;
- Collect all endpoints at the moment the subject exits from the study, if the subject agrees (primary and secondary endpoints, safety assessments); response to treatment will be registered up to 6 months from baseline or disease progression if it occurs before 6 months;
- Schedule further follow-up visits, especially in case of a serious adverse event.

If a subject exits the trial, this will in no way affect the standard care received for KS.
In case of severe adverse events, the investigator must notify the sponsor and monitor the subject for 4 weeks or until return to grade 1 (or to a grade to be determined by the investigator) following the premature termination of treatment. If treatment is stopped prematurely due to a serious adverse event, a serious adverse event report will be sent by mail (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse reaction will be monitored until it is resolved.

5.9.3 Procedure for replacing subjects

If a patient consent is withdrawn then this patient will be excluded from the analysis, except if

the patient allows investigators to use the already collected data for the primary endpoint.
A new patient will be included in order to be able to apply the Simon's Optimal Design. All patients included will be analyzed (Intention to treat Analysis).

5.9.4 Full or partial cancellation of the study

AH-HP (the sponsor) or the Competent Authority (ANSM) may prematurely discontinue all or part of the trial, temporarily or permanently, upon the recommendation of the Data Monitoring Committee in the following situations:

- first, if suspected unexpected serious adverse reactions (SUSARs) are observed, requiring a reassessment of the benefit-risk ratio for the trial;
- if an interim analysis does not show efficacy after the first stage of the study (as planned in the method section);
- similarly, AH-HP, as the sponsor, or the Competent Authority (ANSM) may prematurely cancel the trial due to the discovery of unexpected facts or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved**.**
- AP-HP, as the sponsor, reserves the right to permanently suspend enrolment at any time if the enrolment targets have not been met.

Irrespective of the reason for cancellation of the trial, subjects still enrolled on the trial will be monitored until the end of their participation, as stated by the protocol.

If the study is cancelled prematurely, AP-HP will inform the Competent Authority (ANSM) and the Institutional Review Board of its decision within 15 days, together with justification for the decision and any recommendations from the Data Monitoring Committee.

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Classic or endemic histologically confirmed Kaposi sarcoma (KS) that is progressive, but does not require a systemic therapy ;
- Injectable and measurable disease, defined as:
    - At least 2 cutaneous lesion ≥10mm in its largest diameter, in a not previously irradiated field;
    - At least 2 other cutaneous lesion ≥10mm in their largest diameter available for repeated cutaneous biopsies, in a not previously irradiated field.

NB: Each cutaneous lesion can be replaced by a cluster of small lesions with edge to edge distance <2 mm, if the biggest diameter of each cluster meet the previous criteria.
- Be willing to provide tissue from cutaneous biopsy;
- At least 4 weeks washout for all KS specific therapies including topical treatment, chemotherapy, radiotherapy and immunotherapy including interferon;
- Provide written, informed consent prior to the performance of any study specific procedures;
- Be more than 18 years of age on day of signing informed consent.
- Have a performance status of 0 or 1 on the ECOG Performance Scale.
- Demonstrate adequate organ function:

Haematological : Absolute neutrophil count (ANC) ≥1500/mm^3; Platelets ≥100 000/mm^3; haemoglobin≥ 8 g/dL;
Renal: Serum creatinine ≤ 1.5 x upper limit of normal (ULN), OR calculated creatinine clearance ≥ 40mL/min (using MDRD formula) for subject with creatinine levels > 1.5 x ULN.
Hepatic: AST (SGOT) and ALT (SGPT) ≤ 2.5xULN, serum total bilirubin ≤ 1.5xULN OR direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5xULN.
PT≤1.5; PTT (TCA) ≤1.5
- Female subject of childbearing potential should have a negative serum pregnancy within 72 hours prior to receiving the first dose of study medication
- Have a health insurance.

6.2 Exclusion criteria

- Known history of organ transplantation, including allogeneic stem-cell transplantation, or HIV (HIV 1/2 antibodies detected at selection);
- Symptomatic visceral involvement of KS including brain metastases;
- Active autoimmune disease that requires systemic treatment or has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Patients with vitiligo, type I diabetes mellitus, hypothyroidism, psoriasis non requiring systemic treatment are permitted to enrol;
- Evidence of clinically significant immunosuppression such as the following: primary immunodeficiency state such as Severe Combined Immunodeficiency Disease; concurrent opportunistic infection;
- Receiving systemic immunosuppressive therapy including oral steroid doses > 10 mg/day of prednisone or equivalent within 7 days prior to enrolment;
- Clinically significant cardiac dysfunction (symptomatic heart failure, clinically significant arrhythmia or conduction disorders);
- Active herpetic skin lesions or prior complications of HSV-1 infection (eg, herpetic keratitis or encephalitis);
- Intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use;
- Previous treatment with talimogene laherparepvec or any other oncolytic virus;
- Prior radiotherapy in which the fields overlap the injection sites;
- Prior immunosuppressive, chemotherapy, radiotherapy, biological cancer therapy, or major surgery within 28 days prior to enrollment or has not recovered to CTCAE grade 1 or better from adverse event due to KS therapy administered more than 28 days prior to enrollment.
- Prior therapy with tumor vaccine;
- Received live vaccine within 28 days prior to enrolment;
- Currently treatment with another investigational device or drug study, or less than 28 days since ending treatment with another investigational device or drug study(s);
- Acute or chronic active hepatitis B (HbS Ag detected) or C infection (HCV RNA detected) at inclusion; or active TB (Bacillus Tuberculosis).

- Known additional malignancy that is currently progressing or requires active treatment within the last 3 years. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer;
- Sensitivity to any of the products or components to be administered ;
- Psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial;
- Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial.
- Female subject of childbearing potential who are unwilling to use acceptable method(s) of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec.
- Sexually active subjects and their partners unwilling to use male or female latex condom to avoid potential viral transmission during sexual contact while on treatment and within 30 days after treatment with talimogene laherparepvec. In addition, male participants should not donate sperm from 3 months after last dose.
- Subjects who are unwilling to minimize exposure with his/her blood or other body fluids to individuals who are at higher risks for HSV-1 induced complications such as immunosuppressed individuals, individuals known to have HIV infection, pregnant women, or infants under the age of 3 months, during talimogene laherparepvec treatment and through 30 days after the last dose of talimogene laherparepvec.
- Vulnerable subjects: prisoners incarcerated following administrative or court decision, subjects with psychiatric disorders who are involuntary hospitalized, subjects under legal protection measure, subjects who cannot express their consent.

6.3 Recruitment methods

Justification of sufficient recruitment capacity for the number of subjects that need to be included:
Patients will be recruited in 2 centers of dermatology in France.

	Number of subjects
Total number of subjects to be included	20
Number of sites	2
Enrolment period (months)	18
Number of subjects/site	1-15
Number of subjects/site/month	**0-1**

Expected number of patients eligible in the centers

N°	Name	Last name	Town	Hospital	Expected recruitment/ month	Total
1	Celeste	Lebbe	Paris	Saint Louis – AP-HP	0 to 1	15
2	Nicolas	Dupin	Cochin	Bichat AP-HP	0 to 1	5

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 The investigational medicinal product

Talimogene laherparepvec will be provided as a sterile frozen liquid in a single-use 1.0 ml vial. Each vial will contained talimogene laherparepvec at a nominal concentration of 10^6 PFU/mL or 10^8 PFU/mL in solution for intralesionnal injection.

7.2 Talimogene laherparepvec dosage

Talimogene laherparepvec will be administered by intralesional injection only into injectable cutaneous KS lesions. Talimogene laherparepvec must not be administered into visceral organ. 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 first cycle of talimogene laherparepvec will be 21 days. Subsequent cycles of talimogene laherparepvec will be 14 days.
The maximum volume of talimogene laherparepvec administered at any cycle is 4.0 mL.

At least 2 target cutaneous lesion will be defined at baseline by the investigator to be injected at each cycle (refer to section 8.2, Table 5 and annexe 18.5). Some other target lesions (largest diameter ≥ 1 mm) can be defined and injected upon investigator choice, in accordance with the recommended volume to be injected in each lesion, and the maximal volume of 4 ml at each cycle (cf annexe 18.5).

The recommended volume of talimogene laherparepvec to be injected into KS lesions is dependent on the size of the lesions and should be determined according to the injection volume guideline in Table 2. The tumor size assessment should be done by clinical exam using ruler or caliper for cutaneous and palpable lesions.

Tumor size	Maximum injection volume
> 5 cm	4.0 ml
> 2.5 to 5 cm	2.0 ml
> 1.5 to 2.5 cm	1.0 ml
> 0.5 to 1.5 cm	0.5 ml
≤ 0.5 cm	0.1 ml

Table 2: Recommended volume of talimogene laherparepvec to be injected into KS lesions according to tumor size

At least 2 target cutaneous lesion will be defined by the investigator at baseline to be monitored at each cycle (uninjected lesions) (refer to section 8.2, Table 5 and annexe 18.5).

Injected lesions will be covered by on occlusive dressing for 7 days after injection, if possible (cf annexe 18.6). Patients should be advised to avoid touching or scratching injection sites. Close contacts who are pregnant or immunocompromised should not change the patient dressing or clean their injection sites.

7.3 Dose reduction

Dose reductions with regards to changes in the concentrations of talimogene laherparepvec are not permitted. However, patients may require a reduction in the volume injected due to a disease response or due to local toxicity at the injection site.
However, if in the course of administration of talimogene laherparepvec the subject cannot tolerate the full dose due to an injection-related adverse event such as pain, the total volume given should be recorded, and the reason for intolerance should be documented as an adverse event.

7.4 Dose delay

If talimogene laherparepvec treatment was delayed by > 2 weeks, that dose will be deemed to have been missed and the subject will proceed to the next scheduled treatment visit.
If talimogene laherparepvec dosing is delayed by more than 4 weeks from the date of the planned dose due to the occurrence of an adverse event that is considered related to talimogene laherparepvec (ie, approximately 6 weeks from the previous dose), the subject must be permanently withdrawn from talimogene laherparepvec treatment.

7.5 Authorised and prohibited treatments (medicinal, non-medicinal, surgical), including emergency medications

Prohibited concomitant medications during the selection and treatment phase are following:

- Systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir): subjects who are receiving talimogene laherparepvec may not receive systemic antiherpetic drugs, but may receive a topically administered antiherpetic drug more than 20 cm from a talimogene laherparepvec injection site.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Chronic corticosteroids are not allowed. If the subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) for related toxicities, talimogene laherparepvec dosing must be withheld until the corticosteroid dose has decreased to < 10 mg prednisone daily (or equivalent).
- Topical corticosteroids are not allowed in the body area involved with KS
- Immunosuppressive therapy
- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy
- Investigational agents other than talimogene laherparepvec
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.
All concomitant medications received within 28 days before the first dose of trial treatment and 4 weeks after the last dose of trial treatment should be recorded, respectively during the inclusion and end-of-treatment visit.

7.6 Methods for monitoring compliance with the treatment

Not required as talimogene laherparepvec is injected by the investigator.
However a summary of each target injected lesion and the injected volume will be filled at each cycle.

8 EFFICACY ASSESSMENT

8.1 Description of parameters for assessing efficacy endpoints

The primary endpoint will be the best overall response rate (BORR) defined by the occurrence of complete response or partial response of the injected lesions assessed by the PGA criteria (PGA 0 to 4), occurring between baseline and 6 months or the beginning of any other specific therapy for Kaposi sarcoma if it occurs before 6 months.
For the secondary endpoints, the different aspects of clinical response will be evaluated at each cycle using the ACTG and PGA score (for details see § 4 Description of the trial).

PGA score:

Score and category	Description
0: completely clear	Complete relief of symptoms; 100% of improvement
1: almost clear	Marked improvement of all clinical symptoms as compared with baseline with residual signs (≥90% and <100%)
2: marked improvement	Significant improvement of symptoms (≥75% and <90%)
3: moderate improvement	Moderate improvement between score 2 and 4.
4: slight improvement	Improvement of signs and symptoms as compared with baseline (<50% and ≥25%) but remaining signs of active KS
5: no change	Clinical signs and symptoms unchanged from baseline (+-25%)
6: worse	Clinical signs and symptoms deteriorated from baseline (≥25% of deterioration)

Table 3: PGA score

Clinical response, following PGA criteria will be assessed at cycle 2 (W4) and every 2 cycles during treatment.
PGA score 2 to 4 define partial response ; PGA score 0 to 1 define complete response

ACTG criteria:

ACTG criteria are based on WHO adapted to KS (16). They are validated and have been largely used in HIV-associated KS (17), and more recently in classic KS (18).
Clinical response, defined as complete response, partial response, stable disease or progression will be assessed at cycle 2 (W4) and every 2 cycles during treatment.

Modified AIDS Clinical Trials Group (ACTG) Staging Classification (16,19)

Complete Response (CR)	The absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks. Patients whose only remaining manifestation of KS are pigmented macules could be classified as complete response if malignant cells are absent on biopsy of at least one lesion.
Partial Response (PR)	A 50% or greater decrease in the number and/or size of previously existing lesions, lasting for at least 4 weeks, without the appearance of new lesions or the appearance or worsening of any lesion-associated oedema or effusion during this time. A classification of PR requires that the product of the bidimensional diameters in no target lesion increase by >25%. A classification of PR can also be made: - if the sum of the products of the largest perpendicular diameters of the target lesions decreased by >50%, - or if >50% of nodular or plaque-like lesions became macules; - or if >75% of predominantly nodular lesions flattens to indurated plaques - or if criteria for a CR are met but lesion-associated oedema or effusion persist.
Stable Disease (SD)	Any response not meeting the criteria for CR, PR or PD
Progressive Disease (PD)	- An increase of 25% or more in the size of existing lesions - and/or the appearance of new cutaneous or visceral lesions - and/or a change in character from macular to plaque-like or nodular of 25% or more of lesions

Table 4: ACTG criteria

8.2 Anticipated methods and timetable for measuring, collecting and analysing the efficacy data on target lesions

Patients will be monitored at cycle 2 (W4), and every 2 cycles during treatment (once a month) for efficacy assessment (clinical assessment and photographs).

Definition of Kaposi target lesions and cutaneous lesions for biopsies:
Detailed procedures for definition of target lesions are available in 18.5.

	Characteristics	**Number**	**Injection**	**Biopsy**	**Purpose**	**Identification**
Target lesions for	Cutaneous lesion, Progressive,	At least 1	**Yes**	No	For assessment of efficacy on injected lesions	LCI-1

efficacy assessment	≥ 10 mm in its largest diameter *					
	Other cutaneous progressive lesions ≥ 1 mm	*Upon investigat or choice*	***Yes***	*No*	*For assessment of efficacy on injected lesions*	*LCI-2, 3…*
	Cutaneous lesion, Progressive, ≥ 10 mm in its largest diameter*	At least 1	No	No	For assessment of efficacy on uninjected lesions	LCNI
Cutaneous lesions for biopsies	Cutaneous lesion, Progressive, ≥ 10 mm in its largest diameter *	1	**Yes (at least for cycle 1 and 2)**	**Yes, at cycle 3/W6**	For cutaneous biopsies on injected lesions	BI
	Cutaneous lesion, Progressive, ≥ 10 mm in its largest diameter*	1	No	**Yes, at baseline and cycle 3/W6**	For cutaneous biopsies on uninjected lesions	BNI

Table 5: Definition of Kaposi target lesions and cutaneous lesions for biopsy

** or a cluster of small lesions with edge to edge distance <2 mm if the biggest diameter of the cluster is ≥ 10 mm in its largest diameter.*

Kaposi target lesions will be **numbered and photographed**. Their characteristics in terms of **size** (biggest diameter and its perpendicular diameter), **infiltration** (none, papule, nodule), **color**, will be noted. The presence, severity and topography of **lymphedema** will also be noted (Table 6).

Colour photography including total-body photographs, as well as detailed photographs of target lesions, uninjected lesions and any other notable features of the patient's KS, will be taken at baseline/W1, every 2 cycles (once a month) and at the end of study.

Kaposi lesion	**Lymphedema**
Size of target lesions (the biggest diameter and its perpendicular diameter)	**Severity** of lymphedema: 0: no lymphoedema, 1: moderate lymphedema/no embarrassing dressing, 2: embarrassing dressing, 3: painful or oozing
Infiltration 0: none –macule, 1 and 2: papule less or more infiltrated, 3: nodule	**Topography** of lymphoedema
Color: red, purple, brown	**Circumference**

Table 6: Assessment of clinical characteristics of target lesions

- For patients with less than 50 cutaneous lesions: the total number of lesions will be counted at each response evaluation and assessed for nodularity.

- In patients with more than 50 lesions, between one and three representative body areas will be selected, and the total number of lesions within each of those areas will be counted and assessed for nodularity.
- Clusters of small lesions with edge to edge distance <2 mm can be measured as one target lesion.

8.3 Immunologic and virologic analyses

8.3.1 Procedure

Immunologic and viral evaluations will be performed on sequential samples:

Peripheral blood will be collected at 3 time points (at baseline, before the first dose and at week 6/cycle 3/EOT) in one heparinate sample of 20 ml and one EDTA tube.

Skin biopsy will be collected at 2 time points**:** before the first dose (uninjected lesion), at week 6/cycle 3 (one uninjected lesions, and one injected lesions).

For each Kaposi lesion: Two 3mm punch biopsy samples, or one 6 mm biopsy that will be cut in half, will be performed: one is flash-frozen in liquid nitrogen and stored at -80°C, the other is fixed in formalin or AFA. During follow up biopsy should be performed on residual disease, if possible of a same Kaposi lesion, if not of another lesion contiguous to the first lesion.

Please refer to Table 5 **and annexe 18.5 for the distinction between target lesion, biopsy lesion and injected/uninjected lesions.**

8.3.2 Immunovirologic analyses

8.3.2.1 Immunologic analyses

The immunological sub-study will include:

- Characterization of the tumor microenvironnement by immunohistochemistry: immune cells infiltration (quantification of CD3, CD4, CD8, FoxP3+ T cells);
- Analysis of the immunomodulation induced by the treatment on peripheral blood cells: T cells (CD4, CD8, anti-HHV-8 T cells) (flow cytometry, PBMCs)

8.3.2.2 Viral analyses

The HHV8 viral load will be quantified in blood and tumor sample using quantitative real time PCR.
The HSV-1 DNA will be quantified using specific PCR for T-VEC.

9 SPECIFIC COMMITTEES FOR THE TRIAL

9.1 Scientific Committee

- Members

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Scientific investigator Julie DELYON	Dermatologist	AP-HP, Hôpital Saint-Louis	33-1-42-38-53-15 julie.delyon@aphp.fr

Methodologist Matthieu RESCHE-RIGON	Methodologist	AP-HP, Hôpital Saint-Louis	33-1-42-49-97-47 matthieu.resche-rigon@univ-paris-diderot.fr
Others Samia MOURAH	Pharmacologist	AP-HP, Hôpital Saint-Louis	Samia.mourah@aphp.fr 22-1-42-49-48-85
Guislaine CARCELAIN	Immunologist	AP-HP, Hôpital Robert Debré, INSERM 1149 CRI	33-1-42-17-74-94 guislaine.carcelain@aphp.fr
Maxime BATTISTELLA	Pathologist	AP-HP, Hôpital Saint-Louis	33-1-42-49-45-61 maxime.battistella@aphp.fr
Jérôme LE GOFF	Virologist	AP-HP, Hôpital Saint-Louis	33-1-42-49-94-84 jerome.le-goff@aphp.fr

- Missions: elaborate the protocol and eventually decide any modification.
- Operating procedures: Will receive every 6 months a report on enrolments and a report of the steering committee decision and will meet every 6 months or more if necessary.

9.2 Steering Committee

- Members of the committee

Investigators	Specialty	Localisation	Mail	Phone
Céleste Lebbe	Dermatologist	St Louis	celeste.lebbe@aphp.fr	33-1-42-49-46-79
Julie Delyon	Dermatologist	St Louis	Julie.delyon@aphp.fr	33-1-42-49-53-15
Matthieu Resche-Rigon	Methodologist	SBIM St Louis	matthieu.resche-rigon@univ-paris-diderot.fr	33-1-42-49-97-47
Samia Mourah	Pharmacologist	St Louis	Samia.mourah@aphp.fr	33-1-42-49-48-85
Guislaine Carcelain	Immunologist	Robert Debré	guislaine.carcelain@aphp.fr	33-1-42-17-74-81
Maxime Battistella	Pathologist	St Louis	maxime.battistella@aphp.fr	33-1-42-49-45-21
Jérôme Le Goff	Virologist	St Louis	jerome.le-goff@aphp.fr	33-1-42-49-94-84
Houria Mebarek	Project manager	DRCI-Siège	Houria.mebarek@aphp.fr	33-1-44-84-17-16
Laetitia Da Meda	Clinical Research Coordinator	Dermatology St Louis	laetitia.da-meda@aphp.fr	33-1-42-49-93-92
El-Mountacer El Abbassi	Clinical Research Coordinator	DRCI-URC St Louis	el-abbassi.el-mountacer@univ-paris-diderot.fr	33-1-42-38-53-23

- Missions: check for enrolments, procedures, and review of safety data (toxicities);

- Operating procedures: meeting on site (or TC for those who cannot join) every 3 months and receive every 3 months a report on enrolments, evaluations and side effects from the sponsor

10 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY

10.1 Safety endpoints

Safety is a secondary endpoint.
The occurrence of adverse events will be collected at each visit during the study period. Each adverse event will be named and graded according to the CTCAE v5.0, and defined as linked or not to study treatment.

10.2 Management of special adverse events

10.2.1 Herpetic infection

In clinical studies, herpetic infections have been reported in patients treated with talimogene laherparepvec: oral herpes (5%), keratitis (<1%)
Patients who develop herpetic infections should be advised to follow standard hygienic practices to prevent viral transmissions.
Talimogene laherparepvec is sensitive to acyclovir. The benefit-risk ratio should be considered before administrating acyclovir or other anti-viral agents as it may interfere with the effectiveness of talimogene laherparepvec.

10.2.2 Cellulitis at the injection site

Necrosis or ulceration of tumor tissue may occur during treatment (5%). Cellulitis and bacterial infection have been reported. Careful would care and infection precautions are recommended.

10.2.3 Impaired healing at the injection site

Talimogene laherparepvec may increase the risk of impaired healing in patients with underlying risk factors (eg, lesions in poorly vascularized area). Consider the risk and benefits of talimogene laherparepvec before continuing treatment if persistent infection or delayed healing develops.

10.2.4 Immune-mediated events

In clinical studies, immune-mediated events including gromerulonephritis, vasculitis, pneumonitis, worsening psoriasis, and vitiligo (<1%) have been reported in patients treated with talimogene laherparepvec.
These events should be managed as usually required and the benefit risk ratio of talimogene laherparepvec should be discussed before continuing treatment (see below).

10.2.5 Plasmocytoma at the injection sites

Plasmocytoma has been reported in proximity to the injection sites (<1%). The benefit risk ratio of talimogene laherparepvec should be discussed before continuing treatment.

10.2.6 Obstructive airway disorder

Obstructive airway disorder has been reported following talimogene laherparepvec. Use caution when injecting lesions close to major airways.

10.2.7 Deep vein thrombosis

Deep vein thrombosis has been reported in 1% of patients and should be managed as usually required.

10.2.8 Flu like syndrome

90% of patients experienced influenza-like symptoms. Pyrexia, chills, and influenza like illness, which can occur any time during treatment, generally resolved within 72 hours. These events were reported more frequently within the period of the first 6 treatments, particularly in patients who were HSV-1 negative at baseline.
This syndrome can be prevented by the administration of paracetamol 1g orally at least 1h before the first injection of talimogene laherparepvec.

10.2.9 Accidental exposure of close contacts or HCPs

Accidental exposure may lead to transmission of Imlygic and herpetic infection. Healthcare professionals and close contacts (e.g. household members, caregivers, sex partners or persons sharing the same bed) should avoid direct contact with injected lesions or body fluids of treated patients during the entirety of the treatment period and up to 30 days after the last treatment administration. Accidental needle stick and splash-back have been reported in healthcare professionals during preparation and administration of Imlygic.
Close contacts who are pregnant or immunocompromised should not change the patient's dressing or clean their injection site. Pregnant women, neonates, and immunocompromised individuals should not be exposed to potentially contaminated materials.
Healthcare professionals should ensure that patients are able to comply with the requirement to cover injection sites with occlusive dressings. Patients should also be advised to avoid touching or scratching injection sites as this could lead to inadvertent transfer of Imlygic to other areas of their body or to their close contacts.
Although it is not known if Imlygic could be transmitted through sexual contact, it is known that wild-type HSV-1 can be transmitted through sexual contact. Patients should be advised to use a latex condom during sexual contact to prevent possible transmission of Imlygic. Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with Imlygic (see section 4.6).
Caregivers should be advised to wear protective gloves when assisting patients in applying or changing occlusive dressings and to observe safety precautions for disposal of used dressings and cleaning materials (see sections 4.2 and 6.6).

In the event of an accidental exposure to talimogene laherparepvec, exposed individuals should be advised to clean affected area thoroughly with soap and water and/or a disinfectant. If signs or symptoms of herpetic infection develop, they should contact their physician for examination and treatment if required, as talimogene laherparepvec is sensitive to acyclovir.
Patients, close contact or HCP with exposure to product and herpetic lesions should have swab collections from suspected lesions (ideally within 3 days of appearance of symptoms) for qPCR testing after given consent, and qPCR result will be collected by the investigator and sponsor.

10.3 Rules for delay or discontinuation of talimogene laherparepvec administration

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

• grade 2 or greater immune-mediated adverse events (with the exception of vitiligo and endocrine irAEs which do not require delay in TVEC administration)
• grade 2 or greater allergic reactions;
• any other grade 3 or greater hematologic or non-hematologic toxicity.

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

- A grade 2 or greater immune-mediated adverse event (with the exception of vitiligo or endocrine irAEs) or allergic reactions attributed to talimogene laherparepvec that would require a dose delay of greater than 4 weeks from the date of the planned dose (ie, approximately 6 weeks from the previous dose). NOTE: immune-mediated glomerulonephritis, vasculitis, and pneumonitis and exacerbation of psoriasis have been observed in subjects receiving talimogene laherparepvec in clinical trials. Most of these subjects had a history of other autoimmune disease and/or prior treatment with agents that offered plausible alternative etiologies, however, immune-mediated adverse events can potentially involve any organ system.
- Any other talimogene laherparepvec-related non-hematologic or hematologic toxicities grade 3 or greater occur that, in the opinion of the investigator, would require a dose delay of greater than 4 weeks from the date of the planned dose (ie, approximately 6 weeks from the previous dose).
- If the subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection).

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

10.4 Recording and reporting adverse events

10.4.1 Definitions

According to Article R1123-46 of the French Public Health Code:

- **Adverse event**

Any untoward medical occurrence in a trial subject, which does not necessarily have a causal relationship with the clinical trial or with the investigational product.

- **Adverse reaction to an investigational medicinal product**

Any adverse event occurred in a trial subject, which has a causal relationship with the clinical trial or with the investigational medicinal product

- **Serious adverse event or reaction**

Any adverse event or reaction that at any dose of medication, results in death, threatens the life of the research subject, requires hospitalisation or prolongs hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product, whose nature, severity, frequency or outcome is inconsistent with the safety information described in the Reference Safety Information (summary of product characteristics, or the investigator's brochure if the product is not authorised).

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for clinical trial sponsors (ANSM):

- **Emerging safety issue**

Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials..
For the clinical trials involving the first administration or use of an investigational medicinal product in healthy volunteers, any serious adverse reaction.
Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction
b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial that are notified by the investigator to the sponsor together with follow-up reports
c) any new safety issue relating to the conduct of the clinical trial or the development of the investigational medicinal product, that may impact the safety of the trial subjects.
Examples:

- a serious adverse event likely to be related to the interventions and the trial's diagnostic procedures and which may impact the conduct of the clinical trial,
- a significant risk on the trial subjects such as ineffectiveness of the investigational medicinal product in treating a life-threatening illness under investigation,
- significant safety results from a recently completed non-clinical study (such as a carcinogenicity study),
- the premature termination, or temporary suspension, of a trial conducted on the same investigational medicinal product in another country, for safety reasons,
- an unexpected serious adverse reaction associated with a non-experimental medication required for the conduct of the clinical trial, (e.g. challenge agents, rescue treatment)

d) recommendations from the Data Safety Monitoring Board (DSMB), if applicable, that may affect the safety of the trial subjects
e) any suspected unexpected serious adverse reaction (SUSAR) reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication.

10.4.2 The role of the investigator

- The investigator must **assess the seriousness criteria of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF). The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

- The investigator must **assess the severity** of the adverse events by using a severity grading scale for adverse events, Common Terminology Criteria for Adverse Events [National Cancer Institute].
- The investigator must assess the **causal relationship** between the serious adverse events and the investigational medicinal product, talimogene laherparepvec.

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not ruled out).

These terms are defined as follows (extracted from the WHO-UMC causality categories, version dated 17/04/2012):

Causality term	Assessment criteria*
Certain	· Event or laboratory test abnormality, with plausible time relationship to drug intake ** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable / Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake ** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake ** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

Table 7: WHO-UMC causality categories (extract)

*All points should be reasonably complied with
** Or study procedures

10.4.2.1 Adverse events that require a notification without delay by the investigator to the sponsor

10.4.2.1.1 Serious adverse events

As per article R.1123-49 of the French Public Health Code (CSP), the investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any serious adverse event which occurs during a trial as described in Article L.1121-1(1) CSP, except those which are listed in the protocol (see section 10.4.2.2) and in the investigator's brochure as not requiring a notification without delay.

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

10.4.2.1.2 Adverse events judged as "medically significant"

10.4.2.1.3 Accidental exposure to talimogene laherparepvec and herpetic event

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:

*** Accidental Exposure of HCPs** 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 the Sponsor.

*** Suspected Herpetic Events**

Reporting is required for:

- (1) suspected herpetic events in treated patients;
- (2) suspected herpetic events in at risk HCPs with direct or indirect exposure
- (3) suspected herpetic events in treated patient's close contacts.

If possible, in addition to reporting these events, suspected herpetic lesions should be swabbed and submitted for qPCR testing for the detection of talimogene laherparepvec. Samples should be collected using appropriate technique and a flocked swab from site supplies. This test is likely to be more reliable if performed within the first three days of symptom appearance, however, all lesions should be swabbed, regardless of the timing of presentation.

10.4.2.1.4 In utero exposure

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any pregnancy that occurs during the trial, even if not associated with an adverse event.

10.4.2.1.5 Exposure via breastfeeding

Exposure via breastfeeding occurs if an infant or child could have been exposed *via* the breast milk of a mother being treated with an investigational medicinal product.

Even if such exposure is not associated with an adverse event, the investigator must always notify the sponsor without delay on the day when the investigator becomes aware of any exposure via breastfeeding.

10.4.2.2 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are simply recorded in the case report form. A CRF extraction of these serious adverse events will be realized every 6 months.

- Normal and natural evolution of KS
    - Scheduled hospitalization to monitor the disease being studied (KS),
    - Hospitalization for routine treatment or monitoring of the disease being studied (KS)
    - Disease progression without life-threatening condition
- All adverse effects related to the administration of the investigational medicinal products that are inferior to grade 3 according to CTCAE, or inferior to grade 2 for allergic reaction

- Special circumstances
    - Hospitalization for a preexisting condition,
    - Hospitalization for medical or surgical treatment planned before the research,
    - Transition to the emergencyward lower than 12 hours,
    - Hospitalization for a social or an administrative reason.
- Adverse events during the trial possibly related with the treatments prescribed as part of the patient's standard care

  The investigator must report these events to his Centre Régional de Pharmacovigilance (CRPV).

10.4.2.3 Period during which the investigator must send notification of SAEs to the sponsor without delay

The investigator notifies the sponsor without delay of all the serious adverse events listed in the corresponding section:

- starting from the date on which the subject begins treatment with the investigational medicinal product;
- throughout the whole follow-up period intended by the study;
- until 4 weeks or more after the end of the subject's treatment with the investigational medicinal product.
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear at long term after exposure to the medication, such as cancers or congenital abnormalities).

10.4.2.4 Procedures and deadlines for notifying the sponsor

The investigator should initially complete a SAE reporting form (contained in the case report form). This report must be signed by the investigator.
The investigator must complete every section of the SAE form so that the sponsor can carry out the appropriate assessment.
The initial report sent to the sponsor must be rapidly followed up by one or more additional written reports describing the course of the event and any complementary information.
Whenever possible, the investigator will provide the sponsor with any documents that may be useful for medical assessment of the case (medical reports, laboratory test results, results of additional exams, etc.). These documents must be anonymized. In addition, the investigator must state the study acronym and the number and initials of the study participant on each paper.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has terminated his participation in the trial.

The initial report, the SAE follow-up reports and all other documents must be sent to the sponsor's safety Department by mail (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to **+33 (0)1 44 84 17 99** only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

- The investigator completes the SAE report form in the e-CRF, then validates, prints and signs the form before sending it by mail;

- In case of failure to connect to the e-CRF, the investigator should complete, sign and send the SAE report form to the safety Department. As soon as the connection is restored, the investigator must complete the SAE report form in the e-CRF.

The investigator must comply with all requests for additional information from the sponsor.
For all questions relating to an adverse event report, the safety Department can be contacted via email at vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the initial notification and follow-up report forms for pregnancy exposure during trial participation".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy ends, and must notify the sponsor of the outcome of the pregnancy, using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy report form, the SAE follow-up forms and any other documents will be sent to the sponsor using the same modalities as described above.
If it was the father who was exposed, the investigator must obtain the mother's permission before collecting information about the pregnancy.

10.4.3 Role of the sponsor

The sponsor, represented by its safety Department, shall continuously assess the safety of the investigational medicinal product throughout the trial.

10.4.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all reported adverse events,
- the **causal relationship** between these adverse events and investigational medicinal product and any other treatments,
  All serious adverse events for which the investigator and/or the sponsor suspect a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expectedness assessment** of the serious adverse reactions
  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.
  The sponsor, acting through its safety Department, assesses the expectedness of the serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal product, refer to the Investigator's Brochure in Appendix 18.3.

❖ The serious adverse events associated with the study procedures are:
  - For collection of blood samples : none
  - For cutaneous biopsies : pain, bleeding, infection

- For serious adverse events that may be related to the additional medicinal products:
  - For premedication by paracetamol: refer to the SmPC for the specialty used
  - For local anesthesia (before each cutaneous biopsy and/or before each injection of the investigational medicinal product): refer to the SmPC for the topical anaesthetic agent used (ex: topical lidocaine or injectable xylocaine)

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM (French Health Products Safety Agency).

- The sponsor must send the initial report without delay upon receipt of the unexpected serious adverse reaction if it is fatal or life-threatening, or otherwise within 15 days from receipt of any other type of unexpected serious adverse reaction;
- The sponsor must provide all relevant additional information by sending follow-up reports, within 8 calendar days following receipt.

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

The sponsor must notify all the investigators about any information that could adversely affect the safety of the trial subjects.

10.4.3.2 Analysis and declaration of other safety data

This relates to any new safety data that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.

The sponsor will inform the competent authority and the Ethics committee without delay after becoming aware of the emerging safety issue and, if applicable, describe which measures have been taken.

Following the initial declaration of emerging safety issue, the sponsor will declare to ANSM any additional relevant information about the new safety issues in the form of a follow-up report, which must be sent no later than 8 days after becoming aware of the information.

10.4.3.3 Annual safety report

The sponsor must prepare once yearly throughout the trial duration an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- an analysis of safety data concerning trial subjects
- a description of the patients included in the trial (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- cumulative summary tabulation of all the serious adverse events that have occurred since the beginning of the clinical trial,

The report must be transmitted to ANSM no later than 60 days after the anniversary date corresponding to the date of authorization of the clinical trial by ANSM.

10.4.4 Data Safety Monitoring Board (DSMB)

A DSMB will be set up for this trial. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially as the protocol includes interim analyses). The DSMB must hold its first meeting before the first subject is enrolled. The DSMB's preliminary meeting should take place before the protocol submission to competent health authority (ANSM) and Ethics committee.

The DSMB members are:

Pr MARCELIN Anne-Geneviève	Virologie	Sorbonne Université-AP-HP	anne-genevieve.marcelin@aphp.fr
Dr BOUTBOUL David	Immunohématologie	Université de Paris	david.boutboul@aphp.fr
Dr COUFFIGNAL Camille	Epidemiologie, biostatistiques et Recherche Clinique	P-HP URC-BICHAT	camille.couffignal@aphp.fr

11 DATA MANAGEMENT

11.1 Data collection

The investigator will permit the sponsor's representatives to monitor the study at the frequency defined in the contract, depending on enrolment at each centre.

Case Report Forms (CRFs) and related source documents will be reviewed in detail during monitoring visit (completeness, adherence to the guidelines, accuracy compared to source documents). The sponsor's representative will also review regulatory documents, drug storage and accountability.

The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by sponsor's monitors or representatives of other regulatory agencies.

Identification of data collected directly in the CRFs will be considered as source data.

11.2 Right to access source data and documents

11.2.1.1 Access to data

In accordance with GCP:

- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures.

- the investigators will ensure the persons in charge of monitoring and auditing the clinical trial and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.2.1.2 Source documents

The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the trial. Source documents will be kept by the investigator, or by the hospital in the case of hospital medical records, for the statutory period.

Source documents are mainly medical files, photography and laboratory test results.

11.2.1.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal product, the study, the study participants and in particular the identity of the participants and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the French Criminal Code).
During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymized.
Under no circumstances will the names and addresses of the subjects be shown.
Only the subject's initials will be recorded, along with an identification code specific to the study indicating the order of enrolment.
The sponsor will ensure that each subject has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.3 Data processing and storage of documents and data

11.3.1 Identification of the data processing manager and the location(s)

The management of data processing is held by Clinical Research Unit of Saint Louis hospital under the responsibility of Pr Matthieu Resche-Rigon, SBIM, Hôpital Saint-Louis, 1 avenue Claude Vellefaux, 75010 PARIS.

11.3.2 Data entry

Data will be entered electronically via a web browser.

11.3.3 Data processing (CNIL, the French Data Protection Authority) in France

This trial is governed by the CNIL "Reference Method for processing personal data for clinical studies" (MR-001, amended). AP-HP, the study sponsor, has signed a declaration of compliance with this "Reference Method".
All personal data for this trial will be processed in accordance with Chapter IX of the amended French Data Protection Act of 6 January 1978 (articles 53-61).

11.3.4 Archiving

The specific documents for a clinical trial on a medicinal product for human use will be archived by the investigator and the sponsor for 15 years after the end of the trial.

This indexed archiving includes, in particular:

- A sealed envelope containing the originals of all information sheets and consent forms signed by all individuals at the site who participated in the study for the investigator;
- One copy of all the information sheets and signed consent forms signed for all individuals at the site who participated in the study for the sponsor;
- "Study" binders for the Investigator and the sponsor, containing:
    - all successive versions of the protocol (identified by version no. and date), and its appendices
    - the ANSM authorisations and CPP decisions
    - correspondence
    - the enrolment list or register
    - the appendices specific to the study
    - the final study report
- The data collection documents

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11.4 Ownership of the data

AP-HP is the owner of the data.
The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

12.1 Planned statistical methods, including the timetable for any planned interim analyses

This is a multicenter non-randomized phase II study, based on a **2-stage phase II Simon's Optimal Design**. The main endpoint is the Best Overall Response Rate (BORR) defined by the occurrence of complete response or partial response following PGA criteria (PGA 0 to 4) recorded from the start of treatment until 6 months or the beginning of any other specific systemic therapy for KS if it occurs before 6 months
The design was developed to test the null hypothesis that the BORR of CR or PR, $P \leq 0{,}100$ versus the alternative that $P \geq 0{,}400$. This a two stage design; after testing the drug on 9 patients in the first stage, the trial will be terminated if 1 or fewer respond and will continue if 2 or more patients respond. If the trial goes on to the second stage, a total of 20 patients will be studied. If the total number responding is less than or equal to 4, the drug is rejected.
Between the 2 stages, inclusions could be suspended until the observation of the BORR at 6 months of the last included patient of the first stage. Nevertheless, if 2 CR or PR are observed before patients 9 no stopping in the inclusions is required.

- **Description**

As a general strategy, continuous efficacy and safety endpoints will be summarized using summary measures (median and interquartile range). Frequency distributions (counts and percentages) will be used to describe categorical endpoints. Similarly, characteristics of patients will be presented using summary measures (median and interquartile range for quantitative characteristics and counts and percentages for categoriel characteristics).

- **Interim analysis**

The interim analysis will be based on the first successively included 9 patients, when their response will be recorded (at most 6 months after study inclusion).
According to the design exposed above, interim analysis of efficacy will be based on the observation of Best Overall Response (See Sample size 12.2). Based on our hypotheses, it was computed that 9 patients would be accrued in stage 1. If necessary, inclusion will be stopped during 6 months after the 9th inclusion waiting for the primary endpoint. The trial will stop with conclusion of inactivity if 0 or 1 response is observed in this stage; otherwise, 11 additional patients will be recruited to a total sample size of 20 patients, with at least 5 responses to indicate that the drug is effective enough. If the total number responding is less than or equal to 4, the drug is rejected. In case of two observed responses before the end of stage 1, the stage 2 will directly begin without any stop.

- **Terminal analysis**

It will be based on intent-to-treat principle, that is, all patients will be analysed whatever the treatment has been administered or not unless consent withdrawal.

Primary endpoint
Terminal analysis will be done once all patients have been included and at the end of their follow-up, and data quality checked.
Point estimates with 95% exact confidence intervals (95%CI) will be computed for the BORR.

Secondary endpoint:
1/ Safety endpoints
All Adverse event will be fully described; safety will be assessed in terms of drug toxicity evaluated by clinic and changes in laboratory parameters, and scored according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

2/ Efficacy endpoints
- The Best Overall Response Rate (BORR) of the injected and uninjected target lesions according to the ACTG criteria will be described by count and percentage with their 95% exact Confidence Intervals (95%CI)
- the Best Overall Response Rate (BORR) of the uninjected target lesions according to the PGA criteria will be described by count and percentage with their 95% exact Confidence Intervals (95%CI)
- the response rate of the injected and uninjected target lesions at month 3 and month 6 according to the PGA and ACTG criteria will be described by count and percentage with their 95% exact Confidence Intervals (95%CI)

- the response rate on lymphedema at month 3, month 6 and at best response (as defined by the primary endpoint) will be described by count and percentage with their 95% exact Confidence Intervals (95%CI)
- The time to response, defined as the time to first response (following the primary endpoint) recorded from the start of treatment will be estimated by Kaplan. Median and its 95CI will be given. In case of patient death we will consider competing events (death precluding the occurrence of response); in the latter case, cumulative incidence will be considered and Gray's estimator used.
- the duration of response will be estimated between the date of first response and any disease progression or death or end of the follow up.
- Deaths from any cause

Patients will be censored at the end of follow up. Median and its 95CI will be given using Kaplan Meier estimator.

Analyses will be performed on SAS (SAS Inc, cary, NC) and/or R (http://www.R-project.org/) software packages.

12.2 Hypotheses for calculating the required number of subjects, and the result

The optimal two-stage design to test the null hypothesis that the BORR equal to CR or PR P ≤ 0,100 versus the alternative that P ≥ 0,400 has an expected sample size of 11,48 and a probability of early termination of 0,775. If the drug is actually not effective, there is a 0,035 probability of concluding that it is (the target for this value was 0,050). If the drug is actually effective, there is a 0,098 probability of concluding that it is not (the target for this value was 0,100). After testing the drug on 9 patients in the first stage, the trial will be terminated if 1 or fewer respond and will continue if 2 or more patients respond. If the trial goes on to the second stage, a total of 20 patients will be studied. If the total number responding is less than or equal to 4, the drug is rejected.

12.3 State whether subjects who exit the study prematurely will be replaced and in what proportion.

If a patient consent is withdrawn then this patient will be excluded from the analysis except if the patient allows investigators to use the already collected data for the primary endpoint. A new patient will be included in order to be able to apply the Simon's Optimal Design. All patients included will be analyzed (Intention to treat Analysis).

12.4 Anticipated level of statistical significance

As described above the targeted alpha risk was 0.05 and it will be 0.035 according to the 2 stage Simon's design. The targeted power was 0.90 and it will be 0.902.

12.5 Statistical criteria for termination of the study.

Concerning the primary endpoint no missing data is allowed given the chosen design. In case of loss of follow up the LOCF approach will be applied.
Concerning secondary endpoints or patients characteristics, complete case analyses will be performed. Additionally, multiple imputation by chained equation will be considered.

12.6 Method for taking into account missing, unused or invalid data

In case of modification of the statistical plan, the DSMB will be informed and the modification will be fully described and justified.

13 QUALITY CONTROL AND ASSURANCE

Every clinical study managed by AP-HP is ranked according to the projected risk incurred by the study participants using a classification system specific to AP-HP-sponsored clinical trials. This study will classified : D.

13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the trial. The sponsor must have a quality assurance system for monitoring the implementation of the study at the research centres.

For this purpose, the sponsor shall appoint Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study sites, after completing their initial visits. The purpose of monitoring the study, as defined in the Good Clinical Practices (GCP section 5.18.1), is to verify that:

• the research subjects are safe, protected and their rights are being met
• the data being recorded is accurate, complete and consistent with the source documents
• the study is carried out in accordance with the current version of the protocol, with GCP and with all statutory and regulatory requirements.

13.1.1 Strategy for site opening

The strategy for opening the sites is determined using the tailored monitoring plan.

13.1.2 Scope of site monitoring

For this study, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore the sponsor, in agreement with the coordinating investigator, has agreed on a logistical score and impact and the corresponding study monitoring level of: level D.

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCD and in accordance with Good Clinical Practice as well as with the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent

- compliance with the study protocol and its procedures
- quality of the data collected in the case report forms: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

13.3 Case Report Form

All information required by the protocol must be entered in the case report forms. The data must be collected as and when it is obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given instructions for using this tool.
Using on-line case report forms means the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, there are consistency checks to ensure the data are verified immediately upon being entered. The investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result the investigator or any other individual involved in conducting the study failing to comply with the protocol, standard operating procedures, good clinical practice or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.
The sponsor has its own procedures for managing these non-compliances.

13.5 Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the basis of medical secrecy.

An audit can be carried out at any time by independent individuals appointed by the sponsor. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the trial agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study.

13.6 Principal Investigator's declaration of responsibility

Before starting the trial, each investigator will give the sponsor's representative a signed and dated copy of his/her curriculum vitæ and RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will agree to comply with legislation and to conduct the trial in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a declaration of responsibility (standard DRCD document) which will be sent to the sponsor's representative.
The investigators and their co-workers will sign a delegation form specifying each person's role.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing and obtaining consent from the research participants

The study is conducted according to the Declaration of Helsinki, is consistent with the ICH guidelines and the local legally applicable requirements.
In accordance with Article L.1122-1-1 of the French Public Health Code, no research can be carried out on a person without his/her free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code.

The person will be given at least 24 hours between receiving the information and being asked to sign the consent form.

The person's free and informed written consent will be obtained by the investigator, or by a doctor representing the investigator, before the person is enrolled on the trial.

The information sheet and a copy of the consent form, signed and dated by the research subject and by the investigator or the doctor representing the investigator, will be given to the individual prior to being enrolled on the trial.

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining their consent as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form.

14.2 Prohibition of concomitant clinical studies participation and exclusion period after the trial, if applicable

An exclusion period of 1 months will apply after the subject has received the last injection in this trial (wash out period).

Whilst participating in this trial, subjects may not take part in any other clinical study without first speaking to the doctor in charge of this trial. However, subject can participate to any other non-interventional research.

14.3 Compensation for subjects

No compensation is anticipated for participating to the research.

14.4 Legal obligations

14.4.1 The sponsor's role

Assistance Publique Hôpitaux de Paris (AP-HP) is the sponsor of this study and has delegated powers to its Clinical Research and Development Department (DRCD) in order to conduct the study in accordance with Article L.1121-1 of the French Public Health Code. AP-HP reserves the right to terminate the study at any time for medical or administrative reasons. In this case, the investigator will be informed accordingly.

14.4.2 Request for approval from the Institutional Review Board

AP-HP, as sponsor, obtains prior approval from the Institutional s Review Board for its clinical trials of medicinal products for human use, within the scope of the Board's authority and in accordance with statutory and regulatory requirements.

14.4.3 Request for approval from the ANSM

AP-HP, as sponsor, obtains prior authorisation from the ANSM for its clinical trials of medicinal products for human use, within the scope of the ANSM's authority and in accordance with statutory and regulatory requirements.

14.4.4 Declaration of compliance with the MR 001 "Reference Method"

AP-HP, the study sponsor, has signed a declaration of compliance with this "Reference Method".

14.5 Modifications to the trial

Any substantial amendment made to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to implementing the amendment, approval from the Institutional Review Board and authorisation from the ANSM, within the scope of their respective authorities.
The information sheet and the consent form can be revised if necessary, in particular if there is substantial amendment to the study or if adverse reactions occur.

14.6 Final study report

The final study report referred to in CSP Article R.1123-67 is written and signed by the sponsor and the investigator. A report summary, meeting the competent authority’s guidelines, has to be sent to the competent authority and Institutional Review Board within one year of the end of the trial i.e. the end of the participation of the last study participant.

15 FUNDING AND INSURANCE

15.1 Sources of funding for the trial

The trial is funded by Amgen.

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own third party liability as well as the third party liability of all the doctors involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the study participant and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GERLING through BIOMEDIC-INSURE, covering its own third party liability and that of any collaborator (doctor or research staff), in accordance with Article L.1121-10 of CSP.

16 PUBLICATION

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and name the sponsor AP-HP (DRCD); a copy of the publication must be sent to the sponsor (see below for rules governing affiliation, and naming the sponsor and funders).

16.1 Mention of AP-HP affiliation for projects sponsored or managed by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is not important
- However, if the trial is funded by an internal call for tenders at the AP-HP, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon
- The AP-HP institution must feature under the acronym "AP-HP" first in the address, specifically followed by: AP-HP, hospital, department, city, postcode, France

16.2 Mention of the AP-HP manager (DRCD) in the acknowledgements of the text

"The sponsor was *Assistance Publique – Hôpitaux de Paris* (Clinical Research and Development Department)"

16.3 Mention of the funder in the acknowledgements of the text

The source of funding (Amgen) will be named in the publication.

This study has been registered on the http://clinicaltrials.gov/ website under *registration* number 04065152

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18 LIST OF ADDENDA

18.1 List of Investigators

Address of the research location	Title	First name Surname	Telephone / e-mail
AP-HP, Hôpital Saint-Louis, Paris, France	Pr	Julie Delyon Céleste Lebbé	33-1-42-49-46-79 celeste.lebbe@sls.aphp.fr
AP-HP Cochin, Paris, France	Pr	Nicolas Dupin	nicolas.dupin@aphp.fr

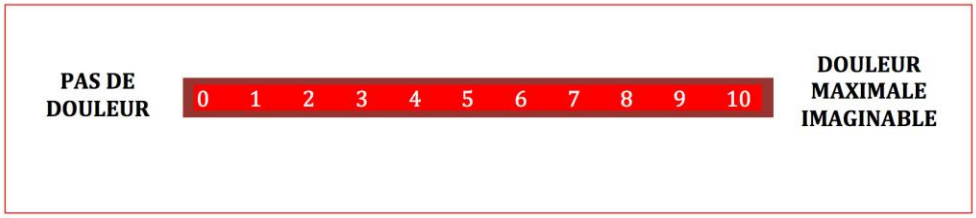
18.2 Serious Adverse Events report form

18.3 Investigator's Brochure

Specify here that the SCP must have been obtained from the EMA website (http://www.ema.europa.eu/ema/), or from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php); otherwise, use the SCP from Vidal.

18.4 Questionnaire or scale

18.4.1 Echelle numérique (pain numeric scale)



18.4.2 ECOG performance status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

18.4.3 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50)
An investigator who is a qualified physician, will evaluate all adverse events as to:

Grade 1	Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

18.4.4 KS-adapted DLQI

Au cours des 7 derniers jours,

1. Votre peau vous a t-elle fait souffrir, brûler ou démanger ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
2. Vous êtes-vous senti(e) gêné(e) ou complexé(e) par votre problème de peau ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
3. Votre problème de peau vous a-t-il gêné(e) pour faire des courses, vous occuper de votre maison ou pour jardiner ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
4. Votre problème de peau vous a-t-il influencé(e) dans le choix de vos vêtements que vous portiez ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
5. Votre problème de peau a-t-il affecté vos activités avec les autres ou vos loisirs ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
6. Avez-vous eu du mal à faire du sport à cause de votre problème de peau ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
7. Votre problème de peau vous a-t-il complètement empêché de travailler ou étudier ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
8. Votre problème de peau a-t-il rendu difficile vos relations avec votre conjoint(e), vos amis ou votre famille ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné
9. Votre problème de peau a-t-il rendu votre vie sexuelle difficile ?
☐ Énormément ; ☐ Beaucoup ; ☐ Un peu ; ☐ Pas du tout ; ☐ Non concerné

Score : Enormément=3 ; Beaucoup=2 ; Un peu=1; Pas du tout=0; Non concerné=0
Total DLQI : 0-27

18.5 Guide investigateur pour l'identification des lésions cibles

Les lésions cibles injectables et non injectables sont définies par l'investigateur avant le 1e cycle, et conservées durant toute l'étude.

	Caractéristiques	Nombre	Injection	Biopsie	Objectif	Identification
Lésions cibles pour suivi de l'efficacité	Lésion cutanée, Evolutive, ≥ 10 mm dans son grand diamètre *	Au moins 1	**Oui**	Non	Mesure de l'efficacité sur une lésion injectée	LCI-1
	Autres lésions cutanées évolutives ≥ 1 mm	*Au choix*	***Oui***	*Non*	*Mesure de l'efficacité sur les lésions injectées*	*LCI-2, 3…*
	Lésion cutanée, Evolutive, ≥ 10 mm dans son grand diamètre *	Au moins 1	Non	Non	Mesure de l'efficacité sur une lésion non injectée	LCNI
Lésions pour biopsies	Lésion cutanée, Evolutive, ≥ 10 mm dans son grand diamètre *	1	**Oui (au moins aux cycles 1 et 2)**	**OUI, au cycle 3/W6**	Prélèvement tissulaire d'une lésion injectée	BI
	Lésion cutanée, Evolutive, ≥ 10 mm dans son grand diamètre *	1	No	**OUI, à baseline et au cycle 3/W6**	Prélèvement tissulaire d'une lésion non injectée	BNI

* Un cluster de lésions de petite taille proches de 2mm maximum peut être utilisé pour représenter une lésion cible, si l'ensemble mesure >10 mm de grand diamètre.

Choix des lésions cibles injectées avant C1

Le nombre minimum de lésions cibles injectées est de 2 (LCI-1, 2,3… et BI).

Celles- ci doivent être : de grand diamètre >10 mm et évolutives. Si plusieurs lésions sont compatibles avec ces critères : les lésions les plus gênantes pour le patient, et les plus facilement injectables, seront choisies.
Le nombre total de lésions injectées est uniquement limité par le volume maximal de T-VEC injectable par cycle (4 ml en tout). Ces autres lésions injectées doivent mesurer au moins 1 mm.

Taille de la lésion injectée	Volume maximal injectable
> 5 cm	4.0 ml
> 2.5 to 5 cm	2.0 ml
> 1.5 to 2.5 cm	1.0 ml
> 0.5 to 1.5 cm	0.5 ml
≤ 0.5 cm	0.1 ml

Il convient d'essayer de définir un maximum de lésions cibles injectées pour traiter un maximum de lésions actives en respectant la limite maximale de 4 ml par cycle.

Exemple : si un patient a 2 lésions principales de 10 et 18 mm qui sont présentes pour les injections, cela représente un volume de 0.5 ml dans la première et 1 ml dans la seconde, soit 1.5 ml en tout. Si le patient possède d'autres lésions actives de Kaposi qui pourraient être traitées, le nombre de lésions cibles injectables peut être augmenté pour atteindre le volume maximal de 4 ml.

- Les lésions cibles injectées sont identifiées « LCI-1, 2, 3 etc ». Elles seront suivies à chaque cycle et traitées jusqu'à 6 mois, ou moins en cas d'arrêt pour toxicité ou de régression complète *.

- « BI » pour « biopsie-injectée » est une lésion injectée qui sera biopsiée au cycle 3. Elle aura été injectée 2 fois au préalable (cycle 1 et 2). Elle ne doit pas être injectée lors du cycle 3 (réalisation de la biopsie). La poursuite des injections au delà du cycle 3 est possible en cas de lésion résiduelle, après cicatrisation complète uniquement.

** La régression complète doit être confirmée histologiquement. Dans ce cas, le volume de T-VEC peut être réalloué à une nouvelle lésion identifiée en cours de protocole, ne faisant pas partie des lésions biopsiables ni sous surveillance (ni BI, ni BNI, ni LCNI). Il convient alors de lui attribuer un nouvel identifiant LCI-chiffre en reprenant la suite de la numérotation, et de le conserver à chaque cycle ultérieur.*

Choix des lésions pour biopsies avant C1

Le nombre de lésions à biopsier est de 2 (BI et BNI).

Celles- ci doivent être : de grand diamètre >10 mm et évolutives. Si plusieurs lésions sont compatibles avec ces critères : les lésions les plus facilement accessibles à une biopsie seront choisies.

- « BI » pour « biopsie-injectée » est une lésion injectée qui sera biopsiée au cycle 3. Elle aura été injectée 2 fois au préalable (cycle 1 et 2). Elle ne doit pas être injectée lors du cycle 3 (réalisation de la biopsie). La poursuite des injections au delà du cycle 3 est possible en cas de lésion résiduelle, après cicatrisation complète uniquement.
- « BNI » pour « biopsie-non injectée » est une lésion jamais injectée. Elle est biopsiée à baseline puis à C3.

Recommandations générales

Les lésions doivent être identifiées et numérotées avant C1 et conserver leur identification pendant toute la durée de l'étude. Elles doivent être identifiées, mesurées et photographiées le cas échéant avant les procédures prévues à chaque visite (injection, biopsie).

18.6 Recommandations pratiques pour l'injection de TVEC

Identification des lésions

Les lésions injectables sont identifiées avant C1 (cf annexe). Leur identification, localisation, taille des diamètres, et photo le cas échéant, doivent être notées avant toute procédure interventionnelle (biopsie ou injection).

Injection du T-VEC en chambre hospitalière

Les professionnels de santé immunodéprimés ou les femmes enceintes ne doivent pas administrer le T-VEC, être en contact avec les sites d'injection ni les fluides corporels des patients traités.
Pour la personne en charge de l'injection du T-VEC au patient, le port d'une blouse de protection ou une blouse de laboratoire, de lunettes de sécurité, et de gants pendant l'administration du T-VEC est obligatoire.
Toutes les plaies exposées avant l'administration devront être recouvertes, et tout contact avec la peau, les yeux ou les muqueuses devra être évité.

Préparer le plateau d'injection

- Des charlottes
- Des lunettes
- Des gants
- Des sur-blouses
- Sac plastiques jaunes (dans lequel tous les éléments utilisés pour les injections seront jetés)
- Une boite à aiguille pour la seringue
- Des pansements et sur-pansements transparents
- De l'alcool

Procédure pour l'injection (faite par l'investigateur):

- Le site d'injection peut être traité préalablement par un anesthésique local (type Emla patch). Un anesthésique injectable peut être injecté à la périphérie de la lésion, mais pas directement dans la lésion.
- Nettoyer la lésion et la zone environnante avec un tampon imbibé d'alcool et laisser sécher
- Injection du TVEC sans jamais retirer la seringue tant que le volume choisi du produit n'a pas entièrement été injecté. À partir d'un seul point d'insertion, injecter le T-VEC le long de plusieurs tracés, aussi loin que la portée radiale de l'aiguille dans la lésion le permet afin d'obtenir une dispersion régulière et complète.

Lésions cutanées

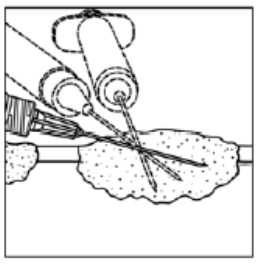


Figure 1.
Administration de l'injection dans les lésions cutanées

- Pour retirer l'aiguille, la faire sortir lentement de la lésion pour éviter un écoulement ou une éclaboussure de T-VEC au point d'injection.
- Répéter ces étapes pour les autres lésions à injecter. Utiliser une aiguille neuve à chaque fois que l'aiguille est retirée complètement d'une lésion et à chaque nouvelle lésion injectée.
- Désinfection de la zone injectée avec un tampon imbibé d'alcool
- Pansement (compresse absorbante puis pansement occlusif sec).

Pansement

Le pansement doit rester 7 jours sans se décoller.
Après administration du T-VEC, les lésions traitées seront protégées à l'aide d'un pansement obstructif (pansement imperméable à l'eau et perspirant, permettant les échanges gazeux) pouvant éventuellement inclure un coussinet absorbant en contact avec la lésion. Ces pansements sont similaires à ceux placés sur la peau lors de la pose de lignes intraveineuses destinées à l'administration de médicaments (aiguille/tube flexible inséré sous la peau).
Le pansement peut être retiré 7 jours après l'injection. Des gants jetables, des écouvillons imprégnés d'alcool et des sacs en plastique seront fournis au patient.

Pour retirer le pansement, vous trouverez ci-dessous les instructions à suivre par le patient et ou le personnel soignant:

- **Retrait du pansement après 7 jours**

- Se laver soigneusement les mains au savon et à l'eau.
- Enfiler les gants jetables
- Ôter doucement le pansement et le placer dans le sac à déchets fourni.
- Retirer les gants jetables en les retournant et les placer dans le sac à déchets.
- Éviter de toucher l'intérieur des gants après les avoir retirés.
- Fermer hermétiquement le sac en plastique et le rapporter au centre. Dans le cas où le patient aura fait les soins à domicile, il doit rapporter le sac à déchets au centre pour destruction via la filière DASRI ou DIB si inactivation des déchets.
- Se laver soigneusement les mains au savon et à l'eau.

Si le pansement se détend ou se détache au cours des 7 jours suivant l'injection, vous trouverez ci-dessous les instructions à suivre pour le personnel soignant ou le patient.

- **Retrait et remplacement du pansement : avant la fin des 7 jours**

- Se laver soigneusement les mains au savon et à l'eau.
- Préparer tous les éléments nécessaires, c'est-à-dire les gants jetables, les écouvillons imprégnés d'alcool, le nouveau pansement et le sac en plastique destiné à recueillir les déchets.
- Enfiler les gants jetables et placer le pansement souillé dans le sac à déchets fourni.
- Nettoyer la zone concernée à l'aide d'un écouvillon imprégné d'alcool et placer ensuite celui-ci dans le sac à déchets.
- Laisser sécher la zone.
- Changer de gants, dans la mesure où les premiers ont été souillés par le pansement retiré, et les placer également dans le sac à déchets.
- Enfiler une nouvelle paire de gants et poser le nouveau pansement selon les instructions. Ne pas toucher le site d'injection en posant le pansement.
- Enlever les gants jetables et les placer dans le sac à déchets.
- Fermer hermétiquement le sac en plastique. Si le patient se charge des soins à son domicile, il doit rapporter le sac à déchets au centre destruction via la filière DASRI ou DIB si inactivation des déchets au préalable.
- Se laver soigneusement les mains au savon et à l'eau.

Que se passe-t-il s'il y a un contact et une transmission ?
Dans l'éventualité d'une exposition professionnelle accidentelle au T-VEC (par exemple, par une éclaboussure dans les yeux ou les muqueuses) durant la préparation ou l'administration, rincer à l'eau propre pendant au moins 15 minutes.
En cas d'exposition à une blessure de la peau ou d'une piqûre d'aiguille, nettoyer soigneusement la zone touchée à l'eau et au savon et/ou avec un désinfectant.
Le T-VEC est sensible à l'aciclovir et d'autres agents antiviraux similaires. L'utilisation d'un de ces agents est possible en cas de développement d'une infection suspectée.

Si une infection herpétique est suspectée, un consentement vous sera remis afin d'obtenir votre autorisation pour collecter un écouvillon de votre lésion et puis son analyse en laboratoire centralisé afin de confirmer si cette lésion est due au T-VEC ou au virus de l'herpès sauvage.

18.7 Questionnaire du patient – Détection des infections herpétiques dans l'entourage

A faire remplir par l'équipe en charge du patient à chaque visite

ID du patient		Visite	
N° du centre		Date de visite	
Nom du centre		Investigateur	

	Oui	**Non**
Est-ce qu'un de vos proches vous a informé(e) d'une exposition au T-VEC ?	☐	☐
Si oui, veuillez indiquer la date de / des exposition(s) :		
Si oui, veuillez indiquer le type exposition rapporté par l'un de vos proches (cocher tous ce qui est applicable): - Contact direct avec une lésion injectée / site d'injection, sans gants - Contact avec l'intérieur du pansement recouvrant la lésion sans gants - Autre (veuillez préciser) :	 ☐ ☐	 ☐ ☐
Si oui, veuillez indiquer qui est le proche (conjoint, enfant, personne aidant…)	☐	☐
Est-ce que votre proche a rapporté des symptômes de type boutons de fièvre/ rougeurs sur le visage, les doigts ou d'autres parties du corps ?	☐	☐
Est-ce que votre proche a rapporté des problèmes oculaires ? (rougeur, douleur, sensibilité à la lumière, vision floue, larmoiement) Si oui, veuillez donner quelques détails:	☐	☐
Est-ce que votre proche a rapporté un ou plusieurs symptômes neurologiques ? (fièvre avec des maux de tête, vomissements, léthargie, symptômes psychiatriques, convulsions, faiblesse, confusion, perte de mémoire) Si oui, veuillez donner quelques détails :	☐	☐

Si la réponse à l'une des questions ci-dessus est oui, vous et votre proche serez contactés par le médecin investigateur pour approfondir l'analyse de ce cas et le prendre en charge.