UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: An Evaluation of the Safety of Escalating Doses of Tc 99m Tilmanocept by Intravenous (IV) Injection and a Comparison to Subcutaneous (SC) Injection in Human Immunodeficiency Virus (HIV) Subjects Diagnosed with Kaposi Sarcoma (KS) – Protocol NAV3-24

This is a clinical trial, a type of research study. Your study doctor(s), Dr. Kieron Leslie and study staff from the UCSF Department of Dermatology will explain the clinical trial to you.

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you have been diagnosed with HIV and also have Kaposi Sarcoma (KS).

Why is this study being done?

The purpose of this research study is to learn if using a tracing agent called Tilmanocept can identify the Kaposi Sarcoma tumor cells in your body when it is administered into your bloodstream by IV injection or into your legs by subcutaneous injection (into the fat layer between the skin and the muscle). This drug is experimental or investigational, which means that it is currently being tested in patients with Kaposi Sarcoma (KS). The study drug has been tested in approximately 15 clinical trials. The study drug is also called Lymphoseek® and is approved by the U.S. Food and Drug Administration (FDA) for use in mapping lymph nodes. The study drug is investigational (being used for research) in this study because it is being used for a different purpose and at a different amount.

Tilmanocept has been tested previously in Kaposi Sarcoma patients, where an injection under the skin was able to identify KS cells in the body.

Patients participating in this study will receive one of 3 potential doses of technetium Tc 99m tilmanocept. The purpose of this study is to find out which dose is the safest and works the best at finding KS lesions (abnormal tissue). There are three groups of participants in this study. All participants will receive the study drug by intravenous (IV) injection on a single occasion. The study drug will travel through your blood stream. Participants in Group 3 will also receive the study drug subcutaneously (into the fat layer between the skin and the muscle) on a single occasion approximately one week prior to the IV injection.

Tilmanocept has attached to it a radioactive substance called technetium 99m. Technetium can be detected by a gamma camera (scan). The Tilmanocept, which binds to your Kaposi Sarcoma tumor cells, can be seen in images (pictures) taken using a SPECT scanner. The SPECT scanner detects the radiation given off by the decay of the Tilmanocept and produces images of where Tilmanocept was located in your body.

How many people will take part in this study?

Up to 14 people will take part in this single center study at UCSF.

Voluntary Participation:

Your decision to participate in this study is entirely voluntary. It is your choice to participate or not. If you choose not to consent, there will be no penalty or loss of benefits to you, and all of the medical care you would normally receive will continue and nothing will change.

You can change your mind later and stop your participation in the study, even if you agreed earlier. Your decision to withdraw from this study will not cause any penalty or loss of benefits to you, nor will it affect the medical care that you would receive. If you decide to withdraw from participation, no additional follow up will be required for the study.

What will happen if I take part in this research study? You will need to have the following exams, tests or procedures to find out if you can be in the main part of the study. Some of these exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

This is a non-randomized dose escalation safety study. All patients will receive one of 3 potential IV doses on a single occasion. Doses will begin starting with the lowest dose and moving to the highest dose. The dose you will receive will be determined by the time at which you are enrolled into the study. Patients in Group 3 will additionally receive one dose subcutaneously (into the fat layer between the skin and the muscle) on a single occasion approximately one week prior to the IV dose.

Study screening procedures will be done at San Francisco General Hospital, 1001 Potrero Avenue, Bldg 90, Ward 92, San Francisco, CA 94143

Visit 1: Screening

- The screening visit will take approximately 1-2 hours and may occur over more than one day. The information gathered during this visit will help your doctor confirm you are an appropriate candidate for the study.
- You will be asked questions about your medical and surgical history, medications and demographic information (such as age, gender, and race).
- You will have a physical examination (routine examination of your body including assessing your height and weight).
- Vital signs, which include assessing your body temperature, blood pressure, heart rate, and breathing rate, will be recorded.
- You will have an ECG (electrocardiogram), which records the electrical activity of your heart.
- Your blood will be taken (about 2 teaspoons) for routine testing.
- Your urine will be collected for routine urinalysis.

- You will be assessed for any areas of swelling.
- You will have an evaluation of your KS. Photographs of any visible KS lesions (abnormal tissue) will be taken.
- If you are able to get pregnant, your blood will be taken for a serum pregnancy test before the study drug injection. If you are pregnant, you will not be able to participate.

If the screening exams, tests and procedures show that you can be in the main part of the study, and you choose to take part, then you will also need the following tests and procedures done that are either being tested in this study or being done to see how the study is affecting your body.

Day 1 (Visit 2): IV Injection of Study Drug, Imaging, and Biopsy for Groups 1 and 2

You will arrive at China Basin for the SPECT Imaging. Study procedures will be done at UCSF China Basin Imaging Center at 185 Berry St. Suite 180 and 190, Lobby 6, San Francisco, CA 94107.

Before Injection

- If you are able to get pregnant, you must have a negative urine pregnancy test within 48 hours before the tilmanocept injection. If you are pregnant, you will not be able to participate.
- Your vital signs will be repeated.
- You will be asked about any changes in your health and medications since your last visit.

Injection of Tc 99m tilmanocept

- You will receive the injection of the study drug through an IV placed in your arm. The amount of the study drug injection is small, less than a teaspoon.

After injection of the study drug at about 30 minutes:

- Your vital signs will be repeated.
- You will have an ECG.

SPECT Scanning:

- You will be imaged at one time point on Day 1 beginning at 60-75 minutes after injection. Your body will be positioned in the large donut-shaped SPECT/CT scanner while you rest lying flat on the scanner bed. The scanning session could take up to 1 hour. The SPECT part of the scanner detects the radiation in the study drug to create a picture of the study drug in your body. The CT part of the scanner uses a small amount of radiation to create a clearer picture of the tumor cells in your body. It is important that during all scans, you keep your body as still as possible. During the scan it will be important that you try to rest quietly with your eyes closed, keeping your head and the rest of your body as still as possible.

After study drug injection and scanning is complete:

- You will be assessed for any adverse events.
- Your blood will be taken (about 2 teaspoons) for safety testing.
    - **Blood drawing:** blood samples will be drawn by inserting a needle into a vein in your arm. A total of about 4 teaspoons will be drawn for the whole study.
- Your urine will be collected for routine urinalysis.

Following injection and imaging procedures, you will travel to San Francisco General Hospital, 1001 Potrero Avenue, Bldg 90, Ward 92, San Francisco, CA 94143.

- A skin biopsy will be taken.
    - A skin biopsy of up to 6 millimeters in size, about the width of a pencil eraser, will be collected from a Kaposi's sarcoma tumor to analyze the tumor cells. The skin around the tumor will be cleaned with iodine solution or other topical antiseptic agent and then an anesthetic will be injected at the site where the biopsy will be taken.
    - This skin will be sent to the lab for testing after injection with Tc 99m tilmanocept. The area from which the biopsy has been removed will then be closed with a suture(s).

Day 1 (Visit 2): Subcutaneous Injection of Study Drug and Imaging for Group 3

You will arrive at China Basin for the SPECT Imaging. Study procedures will be done at UCSF China Basin Imaging Center at 185 Berry St. Suite 180 and 190, Lobby 6, San Francisco, CA 94107.

Before Injection

- If you are able to get pregnant, you must have a negative urine pregnancy test within 48 hours before the tilmanocept injection. If you are pregnant, you will not be able to participate.
- Your vital signs will be repeated.
- You will be asked about any changes in your health and medications since your last visit.

Injection of Tc 99m tilmanocept

- You will receive the injection of the study drug in each your left and right leg. The amount of the study drug injection is small, less than a teaspoon.

After injection of the study drug at about 30 minutes:

- Your vital signs will be repeated.
- You will have an ECG.

SPECT Scanning:

- You will be imaged at two time points on Day 1 beginning at 60-75 minutes and 4-6 hours after injection. Your body will be positioned in the large donut-shaped SPECT/CT scanner while you rest lying flat on the scanner bed. Each scanning session could take up to 1 hour. The SPECT part of the scanner detects the radiation in the study drug to create a picture of the study drug in your body. The CT part of the scanner uses a small amount of radiation to create a clearer picture of the tumor cells in your body. It is important that during all scans, you keep your body as still as possible. During the scan it will be important that you try to rest quietly with your eyes closed, keeping your head and the rest of your body as still as possible.

After study drug injection and scanning is complete:

- You will be assessed for any adverse events.
- Your blood will be taken (about 2 teaspoons) for safety testing.
    - **Blood drawing:** blood samples will be drawn by inserting a needle into a vein in your arm. A total of about 6 teaspoons will be drawn for the whole study.
- Your urine will be collected for routine urinalysis.

Day 7 ± 3 (Visit 3): IV Injection of Study Drug, Imaging, and Biopsy for Group 3

You will arrive at China Basin for the SPECT Imaging. Study procedures will be done at UCSF China Basin Imaging Center at 185 Berry St. Suite 180 and 190, Lobby 6, San Francisco, CA 94107.

Before Injection

- If you are able to get pregnant, you must have a negative urine pregnancy test within 48 hours before the tilmanocept injection. If you are pregnant, you will not be able to participate.
- Your vital signs will be repeated.
- You will be asked about any changes in your health and medications since your last visit.

Injection of Tc 99m tilmanocept

- You will receive the injection of the study drug through an IV placed in your arm. The amount of the study drug injection is small, less than a teaspoon.

After injection of the study drug at about 30 minutes:

- Your vital signs will be repeated.
- You will have an ECG.

SPECT Scanning:

- You will be imaged at one time point on Day 7 ± 3 beginning at 60-75 minutes after injection. Your body will be positioned in the large donut-shaped SPECT/CT scanner while you rest lying flat on the scanner bed. The scanning session could take up to 1 hour. The SPECT part of the scanner detects the radiation in the study drug to create a picture of the study drug in your body. The CT part of the scanner uses a small amount of radiation to create a clearer picture of the tumor cells in your body. It is important that during all scans, you keep your body as still as possible. During the scan it will be important that you try to rest quietly with your eyes closed, keeping your head and the rest of your body as still as possible.

After study drug injection and scanning is complete:

- You will be assessed for any adverse events.
- Your blood will be taken (about 2 teaspoons) for safety testing.
    - **Blood drawing:** blood samples will be drawn by inserting a needle into a vein in your arm. A total of about 6 teaspoons will be drawn for the whole study.
- Your urine will be collected for routine urinalysis.

Following injection and imaging procedures, you will travel to San Francisco General Hospital, 1001 Potrero Avenue, Bldg 90, Ward 92, San Francisco, CA 94143.

- A skin biopsy will be taken.
    - A skin biopsy of up to 6 millimeters in size will be collected from a Kaposi's sarcoma tumor to analyze the tumor cells. The skin around the tumor will be cleaned with iodine solution or other topical antiseptic agent and then an anesthetic will be injected at the site where the biopsy will be taken.
    - This skin will be sent to the lab for testing after injection with Tc 99m tilmanocept. The area from which the biopsy has been removed will then be closed with a suture(s).

Safety Telephone Follow-Up (7±3 days after IV injection for all Groups)

- You will be asked about changes in your health and medication.
- You will be asked about any adverse events.

How long will I be in the study?

The screening period begins after you have signed this consent form. A follow-up telephone call will occur 7 ± 3 days after you have received IV injection of the study drug. Total participation may last up to 18 hours over the course of up to 50 days.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from Tilmanocept can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

While the possibility of adverse (bad) reactions happening during this study is very low, it is possible that you may experience adverse or allergic reactions or discomfort. Every person taking part in the study will be watched carefully for any side effects or allergic reactions. Doctors don't know all of the side effects that might happen. It is important that you talk to your study doctor about any changes in health that you experience while taking part in this study. All side effects or changes in your normal health should be reported, even those changes you might not consider to be important.

In other clinical trials with the study drug, no patients experienced serious adverse reactions and the most common adverse reactions were injection site irritation and/or pain (<1%). The study drug has been available commercially for other medical uses since May 2013, and since that time over 250,000 patients have received this drug. The most commonly reported adverse reactions have been lack of effect (<0.067%), injection site pain (<0.02%) and rash (<0.02%).

- **Blood drawing risks:** Drawing blood may cause temporary discomfort from the needle stick, bruising, infection, and fainting.

- **IV insertion:** IV insertion may cause slight pain or discomfort. You may experience tenderness, warmth, or redness along the vein or at the injection site. Inflammation of the vein is common and may occur after the insertion of the IV catheter (tube). Bruising may occur from an unsuccessful IV insertion or during removal of an IV. In some rare cases, an infection can occur at the IV site.

- **Subcutaneous injection:** Group 3 participants will additionally receive the study drug as an injection into each leg. Injection may cause slight pain or discomfort. You may experience tenderness, warmth, or redness at the injection site. In some rare cases, an infection can occur at the injection site.

- **Radiation risks:**
  This research study involves exposure to radiation from Tilmanocept injections and the SPECT/CT scans. This radiation exposure is not necessary for your medical care and is for research purposes only. The additional amount of radiation that you will receive as a result of participating in this study will be a maximum of approximately 8 mSv, or three times the yearly natural background of radiation in the US, which is 3 mSv (a mSv, or milliSievert, is a measurement of radiation). This amount of radiation may involve a low, lifetime risk of cancer. If you are pregnant or breast feeding, you SHOULD NOT participate in this study. If you have any questions regarding the use of radiation or the risks involved, please consult the physician conducting the study.

- **SPECT/CT scan risks:** SPECT/CT scans involve the risks of radiation (see above).

  Having a CT scan may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia when placed inside the CT scanner, or by lying in one position for a long time. You may feel warm and flushed. Incidental findings may arise as a result of having a CT scan as a part of this study. Any incidental findings will be reviewed with you and your study doctor, and your study doctor will determine appropriate follow-up procedures.

- **Biopsy risks:** The biopsy may be slightly painful and there is a small risk of infection at the biopsy site. If you have any sensitivity to iodine or lidocaine, please notify the study staff as both will be used during the procedure.

- **Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important to understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

  For Men and Women:
  Whether you are a man or a woman, there may be risks to your unborn children. If you take part in this study, you must use an effective birth control method as discussed with your study doctor.
  Examples of birth control methods include:
  - Oral birth control pills
  - Birth control patch
  - Implanted (injectable contraceptive hormones or mechanical products such as intrauterine device)
  - Barrier methods (diaphragm or condoms)
  - Tubal ligation or vasectomy
  - Abstinence (no sexual intercourse)

  You should discuss the method of birth control that is best for you to use during the study.

  Please place your initials in the appropriate box below:

 INITIAL HERE:_____

☐ I am surgically sterile (hysterectomy, tubal ligation or vasectomy) or have gone through menopause.

☐ I understand and agree to use contraception during treatment and for the time recommended by my doctor after the treatment is over.

- **Allergic Reaction Risks**

Sometimes people have allergic reactions to drugs. If you have a very bad allergic reaction, you could die. Some things that happen during an allergic reaction that could be a sign or symptom of a life-threatening allergic reaction (anaphylaxis) are:

- Rash or hives
- Having a hard time breathing
- Wheezing when you breathe
- Inability to breathe without assistance
- Sudden change in blood pressure (making you feel dizzy or lightheaded)
- Swelling around the mouth, throat or eyes
- Fast pulse
- Sweating
- A feeling of dread

You should get medical help and contact the study doctor or staff if you have any of these or any other side effects during the study.

- **Unknown Risks:** The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

- For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

You will not receive any medical benefit as a result of being in this study, but the information obtained in this study may benefit future cancer patients. We do know that the information from this study will help doctors learn more about Tilmanocept as a tracing agent for cancer.

What other choices do I have if I do not take part in this study?

Your other choices may include:

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

Please talk to your doctor about your choices before deciding if you will take part in this study.

How will information about me be kept confidential?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you. Your signed consent form and some of your research tests will be added to your UCSF medical record. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation. Study tests that are performed by research labs and information gathered directly from you by the researchers will be part of your research records but will not be added to your medical record. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Navidea Biopharmaceuticals, Inc.
- Representatives of Navidea Biopharmaceuticals, Inc.
- The University of California
- The National Cancer Institute (NCI) and other government agencies, e.g., the Food and Drug Administration (FDA), involved in keeping research safe for people.

Are there any costs to me for taking part in this study?

No. The sponsor has agreed to pay for all procedures associated with this research study; you or your insurer will not be billed.

Will I be paid for taking part in this study?

You will be paid for the time that is required to complete the study visits. You will receive the following amounts for each completed visit:

Visit 1: $ 75.00
Visit 2: $ 250.00
Visit 3 (Group 3 only): $ 250.00
Safety Telephone Follow-Up: $ 25.00

If you feel that the payment listed may interfere with your making a good decision about whether or not you should volunteer to be in this study, you should not agree to participate. You will be paid at the end of your participation for each completed visit.

You may be required to report the payment received for this study to the Internal Revenue Service as taxable income. You have to provide your social security number because the IRS may be told how much you were paid to take part in this study.

If you withdraw from the study, you will receive a prorated amount for each scheduled visit made to the clinic. A check will be mailed to you about 6-8 weeks after your participation in the study has ended.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Dr. Kieron Leslie, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call her at (415) 206-8680.

> **Treatment and Compensation for Injury:** If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California or the study sponsor, Navidea, depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415- 476-1814.

What are my rights if I take part in this study?

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

What if new information becomes available?

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Are there reasons we might take you out of the study?
Even if you want to stay in the study, there may be reasons we need to take you out of it. You may be taken out of this study if:

- We find out it is not safe for you to stay in the study. For example, your health may worsen or we may find out that the study drug might harm you.
- Your healthcare is not being managed properly or you are not coming for study visits as scheduled
- The study doctor feels it is not in your best interest to continue
- If the sponsor or study doctor decides that the study or your participation should be stopped for any reason

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor(s) Dr. Kieron Leslie at (415) 206-8680.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-1814.

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

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date	Participant's Signature for Consent
Date	Person Obtaining Consent
Date	Witness – Only required if the participant is a non-English speaker

 INITIAL HERE:_____