Kettering Health Network
Kettering, Ohio

INFORMED CONSENT FORM AND AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

Name of Research Study: A Prospective, Randomized, Parallel Group, Double-Blinded Clinical Trial Comparing Lymphoseek and ^{99m}Tc-Sulfur Colloid with Regard to Preoperative Imaging and Imaging Drug Kinetics and Intraoperative Lymphatic Mapping and Sentinel Lymph Node Biopsy Findings in Patients with Known Breast Cancer

Study #: KHNIC-P14-001

Sponsor: Kettering Medical Center

Study Doctor Name: **Arash Kardan, MD**

Research Site Addresses:

Kettering Medical Center
Arash Kardan, MD
3535 Southern Blvd
Kettering, OH 45429

Wright State Physicians
Roxane Weighall, DO
2300 Miami Valley Drive, Suite 350,
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South Dayton Surgeons, Inc.
3533 Southern Boulevard, Suite 2250
Kettering, OH 45429

Daytime Telephone Numbers: Dr. Kardan: 937-395-8611
Dr. Weighall: 937-424-2469
Dr. Sawmiller: 937-534-0330

24-hour Contact Numbers: Dr. Kardan: 937-298-4331
(ask operator to page Dr. Kardan)
Dr. Weighall: 937-424-2469
Dr. Sawmiller: 937-463-1743 (Medical Answering Service)

You should keep a copy of this form. If you have any questions or problems during the study, call the phone number(s) above.

PURPOSE OF THIS FORM
The purpose of this form is to help you decide if you want to be in the research study. It is up to you to decide if you want to take part in this study. You should take part in this study only if you want to.

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

Before you decide if you want to take part in this research study, it is important that you read the information below.

If you sign this form, it means that you agree to take part in this study. This form describes what the study is about and what will happen. It also tells you about the risks and benefits of the study.

You can change your mind about taking part in this study at any time. You may leave the study at any time, even if you have signed this form. You do not have to give a reason.

After reading this form and talking with the study staff, you should know which parts of the study are medical care and which are experimental. Please ask any questions you have.

The sponsor is paying for this research study. Your study doctor will be paid by the sponsor.

When deciding to take part in a research study you should know:

- The main goal of medical care is to help you.
- The main goal of a research study is to gain information to help patients in the future.
- Parts of this study may involve medical care that is routine for you. This routine care, known as standard care, is the treatment normally given for a certain condition or illness.
- Being in this study does not replace your regular medical care.

SOURCE OF FUNDING FOR THE STUDY
Funding for this research study will be provided by Navidea Biopharmaceuticals, the company that makes Lymphoseek®.

PURPOSE OF THE STUDY:
You are being asked to be in this study because you are currently undergoing treatment for breast cancer. One way to learn more about your cancer is to do a sentinel lymph node biopsy (removal). The primary purpose of this study is to see how well one of two

different approved drugs helps us find the sentinel lymph node, which is the first lymph node(s) to which cancer cells are most likely to spread. There can sometimes be more than one sentinel node.

DESCRIPTION OF THE STUDY

This is a research study to compare how well the two study drugs, Lymphoseek® and sulfur colloid, find sentinel lymph nodes. Lymph nodes are small, bean-shaped organs located within the body, throughout the lymphatic system (the tissues and organs involved in immunity, which aids in the fight against infection and cancer). This is a randomized study, meaning you will have a 50/50 chance of receiving either Lymphoseek® or sulfur colloid (hereafter referred to as the Study Drug). Neither you nor your study doctor will know which Study Drug you receive. Both of these Study Drugs are approved for use in detecting sentinel lymph nodes. If you have cancer in both breasts, you will not be randomly assigned but instead will receive injections of both Lymphoseek® and sulfur colloid, one in each breast. You and your study doctor will be blinded to which breast is injected with which Study Drug.

In this research, the Study Drug you are randomized to, along with vital blue dye used during the surgical procedure, will be used as the tracing agents to find the sentinel lymph node(s).

The Study Drug will be injected around the outside edge of the colored area around the nipple, which is called the areola. The injection of the affected breast will occur on the day of your surgery. The vital blue dye may also be injected around the outside edge of the areola at the time of surgery. The amount of each injection is very small, about ½ of a teaspoon. The Study Drug, used as a tracing agent, and vital blue dye will travel through your lymphatic channels to the nearest lymph node. The Study Drug will have a radioactive substance attached that is called technetium 99m. Since technetium is radioactive, it can be detected by a gamma camera (imaging scan) or a hand-held probe, similar to a small Geiger counter. Through this process, the Study Drug will travel through the lymph system and attach to cells in the lymph node(s) to help identify the nodes that drain from your breast. The vital blue dye is visible to your study doctor only during surgery. Your study doctor can identify lymph nodes by the blue color. The lymph nodes identified by the Study Drug and/or vital blue dye will be removed by your study doctor. These nodes will be examined by another doctor (pathologist) to see if your cancer has spread to them.

During and after surgery, your study doctor will continue to check your safety while using the Study Drug and vital blue dye by checking vital signs such as your pulse, breathing rate, heart rate, temperature, and blood pressure, along with doing any physical examinations needed and assessing any side effects that you report to us.

After your surgery, you will be discharged from the hospital as you would normally under your study doctor's guidance. The study nurse will contact you by phone about a week after your surgery to see how you are doing. Your participation in the study is considered completed at that time.

About 40 subjects will take part in this study at Kettering Medical Center.

PROCEDURES
This section will tell what you can expect to happen if you agree to be in the study. You may ask any questions about the study, and then, if you agree to participate, sign this consent form.

After you have signed the consent form, the following procedures will be done:

Visit 1: Informed Consent Visit (Pre-surgery Visit)
This visit will take place at either your surgeon's office or the Innovation, Research & Grants office at Kettering Medical Center.

- You will provide details about your medical history and answer questions from the study doctor. This information helps the study doctor determine your overall health.
- You will be asked to list the medications you have taken over the last 7 days.
- Information from a recent physical exam, including measurements of vital signs (pulse, breathing rate, temperature, and blood pressure) will be recorded for this study.
- Any new questions you've thought of since your doctor first talked to you about this study will be answered.

Visit 2: Administration of the Study Drug (Lymphoseek® or Sulfur Colloid) and Surgery.
This visit will take place at the hospital beginning in the Nuclear Medicine department and then moving to the Surgical Department.

Nuclear Medicine Imaging:

- If you are of childbearing potential, you must have a negative urine pregnancy test in order to be in the study. This test will be done before the Study Drug injection.
- You will be asked about any side effects you have had since your screening visit.
- The Study Drug will be injected by the study doctor on the outside edge of the areola of the affected breast. You will be asked to rate your level of discomfort just prior to the injection and just after the injection using a visual pain rating scale that shows cartoon faces that correlate to a number that goes from 0 for no pain to 9-10 worst pain you have experienced.
- After the injection of the Study Drug, you will have imaging (SPECT/CT) done for detecting the movement of the Study Drug through the tissues. The length of time for the injection procedure and imaging is approximately 60 minutes but may be as long as 150 minutes (2.5 hours).
- During the injection and imaging process, your vital signs and any side effects will be recorded.

Surgery:

- You will be prepared for surgery in the normal manner.
- After the anesthesiologist puts you to sleep, your surgeon will inject the vital blue dye.
- Your surgeon will use a hand-held radiation-detecting probe similar to a Geiger counter to measure the Study Drug in the lymph node(s).
- As part of the surgical procedure, your surgeon will remove one or more lymph nodes for evaluation by the pathologist.
- Your surgeon will complete your surgery and you will be followed in the usual manner as instructed by your surgeon.

Visit 3: Follow-up (After Surgery, by Telephone)

- About a week after your surgery, the study nurse will call you and ask about any side effects you have had since your surgery.

Ask us if you have any questions about the tests and procedures for the study.

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.

WHAT WILL I BE ASKED TO DO IN THIS STUDY?
Before you decide whether to be in this study, you should think about how the tests and study visits will affect your time away from work and your schedule.

To be in this study, you must agree to:

- Follow directions from the study staff.
- Make and keep study appointments.
- Give urine samples as requested.
- Tell the study staff about all of the medicines you have taken for 7 days before beginning the study.
- Tell the study staff about any changes to your health during the study.
- Not be part of any other research study while participating in this study.

RISKS AND DISCOMFORTS
It is possible the drug you are given could cause adverse (bad) reactions or discomfort. You should talk to your study doctor about any side effects that you have while taking part in the study.

You may have a local injection site reaction from the Study Drug including swelling, redness, burning, or itching. These reactions are generally mild and do not require treatment.

In clinical trials of Lymphoseek®, no patients experienced serious adverse reactions and the most common adverse reactions were injection site irritation and/or pain (less than 1%). You should tell your study doctor if you have had any prior bad reactions the drug dextran, as this may make you more likely to have a bad reaction to Lymphoseek®.

Adverse reactions from sulfur colloid that have been reported are rash, allergic reaction, urticaria (hives), severe whole body allergic reaction, and low blood pressure.

Less frequently reported adverse reactions are fatal cardiopulmonary arrest, seizures, dyspnea, bronchospasm, abdominal pain, flushing, nausea, vomiting, itching, fever, chills, perspiration, numbness, and dizziness.

Vital blue dye has been shown to produce an allergic reaction in a small number of people. These reactions may include itching, swelling and in rare instances, shock.

Serious allergic reactions may be life-threatening. You will be monitored to see if you develop this type of reaction. If you do, you will receive prompt treatment.

If the Study Drug along with the vital blue dye does not work, and no sentinel lymph node is identified, all of the lymph nodes in the area may be removed by your study doctor.

The effects of the Study Drug on sperm or egg development or on a developing child are not known. Females wanting to be in this study must not be pregnant or nursing. If you become pregnant while taking part in this study, notify the study doctor at once.

Vital blue dye has also caused a change in color around the injection site that can be seen for up to 48 hours after injection.

The Study Drug uses radiation. Radiation occurs naturally in the environment and is used in treating and examining subjects for medical reasons. Radiation exposure is cumulative (adds up over time). Radiation exposure increases other health risks including cancer. The amount of radiation received from the Study Drug is only slightly more than you would receive from a chest x-ray or about the amount of radiation you are exposed to naturally from the environment over a period of a few months.

In addition to the risks or discomforts listed here, there may be other risks that are currently not known. Also, the risks or discomforts described may occur more often or be more severe than has been seen before.

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.

OTHER RISKS
When taking any new drug, you should be careful until you know how it affects you before you:

- Drive,
- Operate machinery, or
- Need to be alert.

NEW FINDINGS
You will be told about any new information that might change your decision to be in this study. You may be asked to sign a revised consent form if this occurs.

BENEFITS
You may or may not receive a medical benefit from being in the study, depending upon the whether the Study Drug helps guide your surgeon in identifying a sentinel node(s). The information learned from this study may also benefit patients in the future.

COSTS
The Study Drug will be provided to you at no charge. The sentinel node biopsy procedure is considered standard or routine medical practice and it will be charged to you, your insurance company, or third-party provider. Any procedures or tests performed for the study outside of routine medical care for your condition will not be charged to you, your insurance company, or third-party payer. You, your insurance company, or other third-party payers will be billed for all other medicines and/or medical procedures used during the study to treat other medical conditions.

Participating in this research may lead to additional costs to you. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

Ask your study doctor to discuss the costs that will or will not be covered. This discussion should include the costs of treating possible side effects. Otherwise, you might have unexpected expenses from being in this study.

PAYMENT FOR PARTICIPATION
You will be paid $75.00 for completion of each study visit/encounter (Visits 1, 2 and 3), for a total of $225.00 for your participation in this study.

ALTERNATIVE TREATMENT
You do not need to be in this study to receive Lymphoseek® or sulfur colloid to identify sentinel lymph nodes. You can receive the same treatment without being in this study.

HOW WILL MY INFORMATION BE PROTECTED?
All information that you give will be kept strictly confidential. The information collected about you usually will not directly identify you (for example, by name, address, or social security number). Instead, your initials and a code number will be used for your information.

Your records may be reviewed by:

- The study sponsor.
- People who work with the sponsor on the study.
- Government agencies, such as the FDA.
- Copernicus Group Independent Review Board (IRB). The IRB is a group of scientists and non-scientists who review the ethics of research. The goal of the IRB is to protect the rights and welfare of study subjects.

These people may look at your records to make sure the study has been done the right way. They also want to make sure that your health information has been collected the right way, or for other reasons that are allowed under the law.

If information about this study is published, you will not be identified.

There is a risk of loss of confidentiality in research studies. Every effort will be made to protect you and your health information to the extent possible.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

Federal regulations give you certain rights related to your health information. These include the right to know who will receive the information and how it will be used. The study doctor must obtain your authorization (permission) to use or release any health information that might identify you.

What information may be used and given to others?

The study doctor will get your personal and medical information.

For example:

- Past and present medical records.
- Research records.
- Records about phone calls made as part of this research.
- Records about your study visits.
- Information that includes personal identifiers, such as your name, or a number associated with you as an individual.
- Information gathered for this research about:
    - Physical exams.
    - Laboratory, x-ray, and other test results.
- Records about any study drug you received.

Who may use and give out information about you?

The study doctor and the study staff.

Who might get this information?
The sponsor of this research – Kettering Medical Center. "Sponsor" means any persons or companies that are:

- working for or with the sponsor, or
- associated with the sponsor to conduct this research study, such as Navidea Biopharmaceutical, the company funding this research.

Your information <u>may</u> be given to:
- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries, and
- Copernicus Group Independent Review Board.

Why will this information be used and/or given to others?
- to do the research,
- to study the results, and
- to make sure that the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

When will my permission end?
There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

May I withdraw or revoke (cancel) my permission?
Yes. Your authorization will not expire unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date unless you have a side effect related to the study. Information that has already been gathered may still be used and given to others.

If you withdraw from the study but do not withdraw your Authorization, new health information may be collected until this study ends.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

COMPENSATION FOR INJURY

INSTITUTION LIABILITY:
If you experience an illness or injury as a direct result of participating in this study, you may obtain immediate care at Kettering Medical Center. Kettering Medical Center will cover the reasonable and necessary medical expenses to treat such injury or illness. The Study Doctor will determine if the injury or illness was a result of your participation in the study. Kettering Medical Center will pay for your treatment only if the need for treatment was caused by the study procedures. It is important for you to follow the directions of the Study Doctor, your surgeon and the study staff, as well as the information provided in the informed consent. Kettering Medical Center will not pay for injuries due to your personal conduct outside of the study, for lost wages, discomfort, or costs due to the worsening of any underlying condition. It is up to you or your insurance company to pay the costs to treat any medical condition not caused by this study.

You do not give up any legal rights by signing this consent form.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate in this study. If you do participate, you may freely withdraw from the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled. Your decision will not change your future medical care.

Your participation in this study may be stopped at any time by the study doctor without your consent because:

- the study doctor or your surgeon thinks it necessary for your health or safety;
- you have not followed study instructions;
- Kettering Medical Center has stopped the study;
- administrative reasons require your withdrawal;
- or for any other reason.

QUESTIONS

If you have any questions about this research study, you may call the study site. If you think you have an injury or illness from the study drug, contact the study doctor or study surgeon.

Study Doctor Name: Arash Kardan, MD

Study Surgeons: Roxane Weighall, DO
Carol Sawmiller, MD

Daytime Telephone Numbers: Dr. Kardan: 937-395-8611
Dr. Weighall: 937-424-2469
Dr. Sawmiller: 937-534-0330

24-hour Contact Numbers: Dr. Kardan: 937-298-4331
(ask operator to page Dr. Kardan)
Dr. Weighall: 937-424-2469
Dr. Sawmiller: 937-463-1743 (Medical Answering Service)

You should contact the study doctor first if you have questions, complaints, or concerns about the study.

Please call Copernicus Group IRB at 1-888-303-2224 if:

- You want to talk to someone other than the study doctor or study staff.
- You have a hard time reaching the study doctor or study staff.
- You have questions about your rights as a research subject.

Please visit the Copernicus Group IRB website www.cgirb.com for more information about research studies and the role of a research subject.

SUBJECT'S STATEMENT OF CONSENT AND AUTHORIZATION

A Prospective, Randomized, Parallel Group, Double-Blinded Clinical Trial Comparing Lymphoseek and ^{99m}Tc-Sulfur Colloid with Regard to Preoperative Imaging and Imaging Drug Kinetics and Intraoperative Lymphatic Mapping and Sentinel Lymph Node Biopsy Findings in Patients with Known Breast Cancer

I have read the document (or it has been read to me). I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction.

I voluntarily agree to participate in this study.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form I have not given up any of my legal rights.

CONSENT SIGNATURE:

_____ _____
Signature of Subject Date

_____ _____
First and Last Name of Subject (Print) Time of Consent Signature

Study Personnel Statement
The information about the study was described to the subject in language he/she understood.

_____ _____
Signature of Person Obtaining Consent Date

_____ _____
First and Last Name of Person Obtaining Consent (Print) Time