RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Evaluation of Tc 99m Tilmanocept Imaging for the Early Prediction of Anti-TNFα Therapy Response in Patients with Moderate to Severe Active Rheumatoid Arthritis (RA)

PROTOCOL NO.: NAV3-33
WCG IRB Protocol #20216706

SPONSOR: Navidea Biopharmaceuticals, Inc.

INVESTIGATOR: Charles Talakkottur, MD
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United States

STUDY-RELATED PHONE NUMBER(S): 813-874-1852 (24 hours)

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. It explains how your health information will be used for this study and may be used for research in the future and requests your authorization (permission) to use your health information. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

Why is this study being done?
This is a study to see how well a drug called technetium Tc 99m tilmanocept (Lymphoseek®) helps us find inflammation in your joints. You are being asked to be in this study because you are currently undergoing evaluation and treatment for rheumatoid arthritis (RA) and your doctor wants to change your RA medication.

Description of the study
The purpose of this study is to find out how well imaging can predict response to your RA medication. Patients participating in this study will receive 150 mcg of tilmanocept radiolabeled with 10 mCi (370 MBq) of technetium Tc 99m per injection. You will receive 2 injections over the 31-week study, one at each of 2 imaging visits. You will receive a single injection of the study drug by intravenous (IV) injection in your arm on each imaging day. Tilmanocept (study drug) will travel through your blood stream to the sites in your body where you have inflammation.

The study drug is a radioactive mapping drug that sticks to swelling and can be seen with a gamma camera (scan). The camera (scanner) is an instrument that detects the radiation given off by the decay of the study drug and produces images of where the study drug has located in your body. There is no pain associated with the use of the camera.

Participant Selection
In total, up to 672 subjects will take part in this study at up to 50 centers in the United States. You are being asked to participate because your current medication for RA is not working as well as your doctor would like, and your doctor will be starting you on a new medication in about 1 month. Your doctor will explain this change to you in detail.

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, all the medical care you would normally receive will continue and nothing will change. Refusing to take part will not result in any penalty or loss of benefits to which you are otherwise entitled.

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 affect the medical care that you would receive. Withdrawing will not result in any penalty or loss of benefits to which you are otherwise entitled. If you decide to withdraw from participation, no additional follow up will be required for the study.

The research site management does not urge, influence, or encourage anyone who works for the company to take part in a research study. Your participation in this study is completely voluntary. You may withdraw from the study at any time and for any reason. Your decision to not participate in the study, or a decision on your part to withdraw from the study, will have no effect whatsoever on your student/employment status at the research site. You may refuse to participate, or you may withdraw from the study at any time without penalty or prejudice.

Information on Study Drug
The study drug is made by Navidea Biopharmaceuticals, Inc. Navidea is working with your study doctor to test the study drug in patients with rheumatoid arthritis. The study drug has been tested in 18 clinical trials. The study drug is also called Lymphoseek® and is approved by the 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, different route of administration and at a different dose amount.

If I agree to join the study, what will I need to do?
If you choose to participate in this study, after you sign this informed consent document, your participation would include the following procedures and events:

Visit 1: Screening

- The screening visit will take approximately 3 hours and may occur over more than one day. The information gathered during this visit will help your doctor confirm if you are an appropriate candidate for the study.
- You will be asked questions about your medical history, medications, and demographic information (such as age, sex, and race).
- You will have a physical examination (routine examination of your body including assessing your height and weight).

- You will have an evaluation of your joints, including your shoulders, elbows, hands, wrists, and knees.
- Vital signs, which include assessing your body temperature, blood pressure, heart rate, and breathing rate, will be taken.
- Your blood will be taken (about 2.5 teaspoons) for routine testing and for rheumatoid arthritis testing.
- Your urine will be collected for routine urinalysis.
- If you can become pregnant, you will have a urine pregnancy test before the study drug injection. If you are pregnant, you will not be able to participate.
- You will answer some questionnaires about your health.

Visit 2: Injection of Study Drug and Imaging

This visit will take about 2 hours.

- Before injection
  - If you can become pregnant, you will have a urine pregnancy test before the study drug injection. If you are pregnant, you will not be able to participate.
  - You will be asked about any changes in your health and medications since your last visit.
  - Your vital signs, which include your body temperature, blood pressure, heart rate and breathing rate, will be taken.
- Injection of the study drug
  - 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. This injection will take less than one minute.
- After study drug injection (within 30 minutes)
  - Your vital signs, which include your body temperature, blood pressure, heart rate and breathing rate, will be taken.
- Imaging (Scanning)
  - You will have scanning at about 60 minutes after injection. You will be positioned with both hands and wrists lying flat on the scanner while you stand or rest on a chair. The scanner detects the radiation in the study drug to create a picture of the study drug in your hands and wrists. This scan will take up to 15 minutes.
- After scanning is finished
  - Your blood will be taken (about 1.8 teaspoons) for routine testing.
  - Your urine will be collected for routine urinalysis.
  - You will start your new RA medication. Your doctor will explain this change to you in detail.

Visit 3: Safety Follow-Up Telephone Call (5 ± 3 days after Visit 2)

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

Visit 4: RA Clinical Assessments and Injection of Study Drug and Imaging (Week 5 ± 1)
This visit will take about 3 hours.

- At a separate appointment (within 7 days) before you arrive for imaging, you will visit the Rheumatologist's office to complete the following:
  - You will be asked to complete some questionnaires about your health.
  - You will have an evaluation of your joints, including your shoulders, elbows, hands, wrists, and knees.
- Before injection
  - If you can become pregnant, you will have a urine pregnancy test before the study drug injection. If you are pregnant, you will not be able to participate.
  - You will be asked about any changes in your health and medications since your last visit.
  - Your vital signs, which include your body temperature, blood pressure, heart rate and breathing rate, will be taken.
- Injection of the study drug
  - 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. This injection will take less than one minute.
- After study drug injection (within 30 minutes)
  - Your vital signs, which include your body temperature, blood pressure, heart rate and breathing rate, will be taken.
- Imaging (Scanning)
  - You will have scanning at about 60 minutes after injection. You will be positioned with both hands and wrists lying flat on the scanner while you stand or rest on a chair. The scanner detects the radiation in the study drug to create a picture of the study drug in your hands and wrists. This scan will take up to 15 minutes.
- After scanning is finished
  - Your blood will be taken (about 2.5 teaspoons) for routine testing and RA testing.
  - Your urine will be collected for routine urinalysis.

Visit 5: Safety Follow-Up Telephone Call (5±3 days after Visit 4)

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

Visit 6: RA Clinical Assessments (Week 12 ±1)
This visit will take about 1 hour.

- At this visit you will visit the Rheumatologist's office to complete the following:
  - You will be asked about any changes in your health and medications since your last visit.
  - You will be asked to complete some questionnaires about your health.
  - You will have an evaluation of your joints, including your shoulders, elbows, hands, wrists, and knees.
  - Your blood will be taken (less than 1 teaspoons) for RA testing.

Visit 8: RA Clinical Assessments (Week 24 ±1)
This visit will take about 1 hour.

- At this visit you will visit the Rheumatologist's office to complete the following:
  - You will be asked about any changes in your health and medications since your last visit.
  - You will be asked to complete some questionnaires about your health.
  - You will have an evaluation of your joints, including your shoulders, elbows, hands, wrists, and knees.
  - Your blood will be taken (less than 1 teaspoons) for RA testing.

How long will I be in the study?
The screening period begins after you have signed this consent form. Total participation may last up to 31 weeks for a total of 7 visits: 1 screening visit, 2 injection and imaging visits, 4 clinic visits including an assessment of swollen and tender joints, and 2 safety follow-up telephone calls.

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 low, it is possible that you may experience adverse reactions or discomfort. Every person taking part in the study will be watched carefully for any side effects. 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 injected subcutaneously (between the skin and the fat), no patients experienced serious adverse reactions and the most common adverse reactions were injection site irritation and/or pain (less than 1%). The study drug has been available commercially for other medical uses since May 2013, and since that time, over 800,000 patients have received this drug. The most commonly reported adverse reactions have been injection site pain (less than 0.02%) and rash (less than 0.02%).

To date, there have been more than 300 IV injections with the study drug with no adverse drug reactions.

You will receive the study drug through an IV needle in your arm. 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 rare cases, an infection can occur at the IV site.

Your blood will be collected for routine testing and RA testing. You may experience mild pain or discomfort, bruising, or swelling at the site where the blood is drawn. Some people may experience fainting, dizziness or light headedness during or immediately after the blood draw. In rare cases, the puncture site may become infected and cause the site to become red or swollen.

The study drug used in this study will expose you to ionizing radiation. Radiation occurs naturally in the environment and is used in treating and examining patients for medical reasons. The natural radiation we are exposed to all the time from the sun and the earth (natural background radiation) is around 300 mrem each year. In comparison, the equivalent for this study is approximately 3.6 years of exposure to natural background radiation. The total amount of radiation exposure you will receive from the study drug is about 10.8 msv or 1080 mrem. Radiation exposure increases other health risks including cancer. The risk of developing health problems or cancer from this radiation exposure is small, but the risk may be cumulative (adds up over time). If you have additional questions about radiation exposure, or have had additional scans using radiation recently, you should ask to speak to your study doctor.

What if I am pregnant or want to have a baby?
Whether you are male or female, your participation in this protocol includes treatment which may present unknown risks to a fetus or embryo. You must avoid becoming pregnant or avoid causing a pregnancy while you are participating in this study. You should discuss a method of birth control that is best for you to use during the study with your doctor. You should tell your doctor immediately if you or your partner becomes pregnant.

Examples of birth control methods that could be used by you and your partner 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)

For Women:
If you are pregnant, you may not participate in this study. There may be risks to you and your unborn baby. Breastfeeding (nursing) mothers will not be included in this study; the study drug could be passed on to a baby through breast milk.

If you are a female of childbearing potential (able to become pregnant), you will be given a pregnancy test at screening (urine test) and before each injection at no cost.

Tell one of the study doctors right away if:

- You are pregnant
- You become pregnant
- You are breastfeeding

For Men:
We do not know what the study drug could do to your sperm. Should you get a woman pregnant, there could be harm to the unborn baby. You and your partner should use an effective form of birth control if you are having sexual intercourse with a woman of childbearing potential while participating in this trial and for 30 days after the last dose of the study drug during visit 4.

Are there benefits to taking part in this 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 other patients.

What are the costs of taking part in this study
The study drug and all study procedures are at no cost to you. The procedures or tests performed for the study are not part of your routine medical care and will not be charged to you, your insurance company, or third-party payer. Your routine medical care that is not part of this study will continue to be billed to you and your insurance company, or other third-party payers. You can ask your study doctor to confirm the costs that will or will not be covered by the sponsor.

Will I be paid for taking part in this study?
You will receive the amounts below for each completed visit:
Visit 1 Screening $150
Visit 2 after imaging $250
Visit 3 telephone $25
Visit 4 after imaging $250
Visit 5 telephone $25
Visit 6 after imaging $250
Visit 7 telephone $25
Visit 8 after imaging $250
Visit 9 telephone $25

You will be paid at each visit.

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.

Use and disclosure of your personal health information
"Health information" means the health information contained within your medical or other healthcare records, which also includes personal identifying information such as your name, address, or birthdate. The information that we collect from this study will be kept confidential. Believe Clinical Trials will take appropriate steps to keep your personal health information private. However, there is no guarantee of absolute privacy. Any information about you will have a number on it instead of your name. Only the research team at Believe Clinical Trials will be able to link the assigned number to your name.

To do this study, we will use the following kinds of health information:

- Results of the tests and procedures done as part of the study
- Things you tell the researchers about your health and the health of your family who have similar conditions
- Information currently in your medical records as well as information added to your medical records during the course of the study

Your health information will be stored so that researchers can continue to use the data in the future and may be combined with information from other studies to explore and better understand the study drug and rheumatoid arthritis.

In order to ensure the scientific value of the study, other parties will be able to view your study information.

The following parties may view your identifying information:

Navidea Biopharmaceuticals, Inc.

Representatives of Navidea Biopharmaceuticals, Inc.

The Food and Drug Administration (FDA)

The Office for Human Research Protections (OHRP) - a regulatory agency that oversees research in humans

Other governmental agencies, including those governmental agencies in other countries

WCG IRB, An Independent Review Board (IRB) is a group of people that reviews research studies. The main goal of this review is to protect the rights and well-being of the human subjects participating in research studies.

Officials of Believe Clinical Trials

Will the results of this study be shared?
Yes, when the study is finished, the results of this study will be shared with professionals in the research community and with the public. You will not be identified in any of the results of the study.

Can I see all my health information collected in the study?
You can see all the health information collected for the study. However, the scan results of your hands and wrists are experimental and will not be used for clinical decision making. Thus, the results of these scans will not be shared with you.

What if I change my mind about sharing my health information?
Your authorization for researchers to use your health information does not have an end date. However:

- You can choose to take back your authorization for researchers to use your health information. You can do this at any time before or during your participation in the research.
- If you take back your authorization, information that was already collected may still be used and shared with others, but the researchers will no longer be able to collect NEW information about you.

- If you take back your authorization, you will not be able to take part in the remainder of the research study.
- To take back your authorization, you will need to tell the research staff in writing at Believe Clinical Trials 5106 N Armenia Ave, Suite 1, Tampa, Florida 33603

Right to Refuse or Withdraw
You do not have to agree to participate in this study if you do not wish to do so. Refusing to participate will not affect your treatment at Believe Clinical Trials. If you want to stop your participation in this study, you may do so at any time. Withdrawing from the study will not affect your regular care at Believe Clinical Trials. If you need to leave early from the study between Week 12 and Week 24, we will try to schedule a final visit to complete clinical assessments.

What other choices do I have if I do not participate in this study?
The alternative to participating is to not participate. You can have your joints evaluated using other standard imaging methods outside the study.

What happens if I am injured because I took part in this study?
It is important that you tell your study doctor if you feel that you have been injured because you took part in the study. You would receive medical treatment for any injury just as you would if you did not participate in this study.

In the event that you are injured as a direct result of study conduct, the study sponsor will reimburse you for the reasonable medical costs of your medical treatment. In order for the sponsor to reimburse you, the study drug must have been administered in accordance with applicable laws, regulations, and the study plan (protocol) and the costs must not be covered by insurance or any third-party coverage.

Who is paying for the study?
Navidea is paying your study doctor and the hospital to do this study.

What if new information becomes available?
If there is new information or any important new findings that could relate to your willingness to continue your participation in this study, we will tell you.

You can then decide if you still want to be in the study. If the FDA or Navidea makes changes to the study before the study starts, the study staff will try to notify you before you check-in. If changes are made after the study has started, the study staff will tell you about them as soon as they have been approved. You can use this information to decide if you want to stay in the study.

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 do I contact if I have questions or concerns about the study?
If you have any questions, concerns, or complaints about this study or your participation in this study, contact your study doctor:

Dr. Charles Talakkottur 813-874-1852 (24 Hours)

If you have questions about your rights as a research subject or have other questions, complaints, or concerns about the research, you can contact WCG IRB at 855-818-2289 or clientcare@wcgclinical.com.

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.

In the event of an emergency, dial 911 immediately. If you require emergency care, be sure to tell the emergency care provider about your participation in this study. Contact the study doctor as soon as possible.

INFORMED CONSENT:

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. I may contact Dr. Charles Talakkottur if I have any more questions about taking part in this study. I understand that Dr. Charles Talakkottur or the company he/she is employed by is being paid by the sponsor for my participation in this study.

I understand that my participation in this research project is voluntary. I know that I may quit the study at any time without harming my future medical care or losing any benefits to which I might be entitled. I also understand that the investigator in charge of this study may decide at any time that I should no longer participate in this study.

By signing this informed consent document, I have not waived any of my legal rights.

By signing this informed consent document, I acknowledge that I can read, understand, and speak English and that I understand the information in this informed consent document. I understand that my study-related medical records may be reviewed by the company sponsoring the study and by government authorities. I have read and understand the above information. I agree to participate in this study. I understand that I will be given a copy of this signed and dated form for my own records.

IF YOU DO NOT AGREE WITH THE STATEMENT ABOVE, YOU SHOULD NOT SIGN THIS INFORMED CONSENT DOCUMENT.

_____ _____

Study Participant (signature) Date

_____

Participant's Name (print name)

_____ _____

Person who explained this study (signature) Date

_____

Person who explained this study (print name)