RESEARCH SUBJECT INFORMATION AND CONSENT FORM

Title:	A Comparison of Tc 99m Tilmanocept Quantitative Imaging with Immunohistochemical (IHC) Analysis of CD206 Expression in Synovial Tissue from Subjects Clinically Diagnosed with Rheumatoid Arthritis (RA)
Protocol:	NAV3-32
Sponsor:	Navidea Biopharmaceuticals, Inc. 4995 Bradenton Avenue, Suite 240 Dublin, Ohio 43017 United States
Investigator:	XXX XXXX

Investigator Phone Number: «PhoneNumber» or «ERPhone» (for after hours)

Site: **«SiteName»**

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.

Why is this study being done?
This study is being done to determine the ability of technetium Tc 99m tilmanocept (study drug) to find inflammatory cells in your joints with rheumatoid arthritis (RA) and to determine the relationship with the different types of cells present in one of your joints affected by your RA. You are being asked to participate in this study because you are currently undergoing evaluation and treatment for RA.

Description of the study
Patients participating in this study will receive 150 mcg of the study drug radiolabeled with 10 mCi (370 MBq). The study drug will be administered one time through an intravenous (IV) injection in your arm. The study drug is a radioactive mapping drug that binds to certain types of cells and can be seen in images (pictures) taken using a SPECT gamma camera (scan). The SPECT 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.

Participants will also undergo a synovial (joint) tissue biopsy, where small samples of tissue will be removed from the soft tissue surrounding a joint in the hand or wrist to examine the activity of RA. This procedure involves the use of a needle to remove the tissue samples. A small percentage of this patient population has reported small amounts of pain and discomfort after the procedure.

Participant Selection
Up to 24 subjects will take part in this study at up to 10 centers in the United States, United Kingdom, and European Union.

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.

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 RA. The study drug has been tested in approximately 16 clinical trials. The study drug is also called Lymphoseek® and is approved by the Food and Drug Administration (FDA) in the United States and by the European Medicines Agency (EMA) in the European Union 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.

If I agree to join the study, what will I need to do?
Most of the procedures in this study are not part of the routine care that you would normally receive for the evaluation of your RA. The use of tilmanocept is for research and is not part of your routine care.

How long will I be in the study?
Total participation in this study may last up to 45 days. 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 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.
- Your blood will be taken (about 2.5 teaspoons) for routine testing and RA testing.
- Your urine will be collected for routine urinalysis.
- If you are able to get pregnant, your blood will be taken for a serum pregnancy test. If you are pregnant, you will not be able to participate.
- You will have an ultrasound assessment of the hands and wrists to evaluate inflammation.
- You will have an evaluation of your joints including your shoulders, elbows, hands, wrists, and knees.
- You will answer questions about your RA and health.

Visit 2: Administration of Study Drug and Imaging
This visit will take about 2 and a half hours

- Before administration of the study drug:
    - If you are able to get pregnant, you must have a negative urine pregnancy test within 48 hours before the tilmanocept administration. If you are pregnant, you will not be able to participate.
    - You will have an ECG (electrocardiogram), which records the electrical activity of your heart.
    - Your vital signs will be taken.
    - You will be asked about any changes in your health and medications since your last visit.
- Study drug administration

    - You will receive the injection of tilmanocept through an IV placed in your arm. The amount of tilmanocept injection is small, less than a teaspoon.
- After study drug administration (within 30 minutes)
    - You will be assessed for any adverse events
    - You will have an ECG
    - Your vital signs will be repeated
- SPECT Scanning
    - You will have scanning of your hands and wrists at about 60 minutes after injection. Your hands and wrists will be positioned on the scanner bed while you rest sitting. 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 scan should take approximately 15 minutes to complete.
- At the completion of imaging:
    - You will be assessed for any adverse events.
    - Your blood will be taken (about 2 teaspoons) for safety testing.
    - Your urine will be collected for routine urinalysis.

Visit #3: Safety Telephone Follow-Up Call (24-48 hours after Study Drug administration)

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

Visit #4: Synovial Tissue Biopsy
This visit will take about 2 hours to complete

- You will have an ultrasound assessment of the hands and wrists to evaluate inflammation.
- An ultrasound-guided synovial tissue biopsy will be performed on a single joint in the hand or wrist to analyze RA tissue cells. This procedure will be completed via validated ultrasound-guided biopsy methods. The RA tissue obtained from the biopsy will be sent to a lab for further testing.
- You will be asked about any adverse events.

Visit #5 Safety Telephone Follow-up Call (5±2 days post-biopsy)

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

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 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 (<1%). The study drug has been available commercially for other medical uses since May 2013 and since that time about 400,000 patients have received this

drug. The most commonly reported adverse reactions have been injection site pain (<0.02%) and rash (<0.02%).

To date, there have been approximately 280 IV injections with the study drug with no adverse drug reactions.

You will receive the study drug IV 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.

You will receive a biopsy of a selected hand joint, where around 12 samples of small tissue, approximately 1-2 mm^2, will be removed from the joint with a needle. A needle will be placed into the joint under local anesthetic guided by ultrasound scanning. This is performed in a sterile (germ-free) setting. It should be noted that a small percentage of participants in this type of procedure have reported small amounts of pain and discomfort after the procedure, and this can be discussed with your study doctor. The samples of tissue are then taken to the laboratory and used for the research purposes described. The majority of patients have no adverse reaction to the procedure, and it is generally well tolerated. Approximately 15% of patients will have minor discomfort after the procedure. Discomfort, swelling/bruising, or worsening of RA have been observed from this procedure, and this can be discussed with your study doctor. Other possible complications which are uncommon include infection of the joint or skin, bleeding, pain, and rarely nerve or tendon damage (less than 1:100,000 risk). The synovial biopsy procedure used in this study is not considered a part of routine RA management; however, the technique is very well tolerated in those who have chosen to participate, and the doctors performing the procedure are fully trained.

Your blood will be collected for routine 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 also 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 or 3mSv. The radiation from the study drug (2.7mSv/266mrem) is approximately equal to 10.6 months of exposure to natural background radiation. 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 will happen to any samples I give?

All blood and urine samples that are taken for the purposes of this study will be analyzed at the hospital where you are participating in this trial and will not be stored for further analyses.

All biopsy tissue samples that are taken for the purposes of this study will be sent to the Centre for Experimental Medicine and Rheumatology at Queen Mary University of London (QMUL) for analysis. Following completion of the study, they will be stored at the bio-bank facility at Experimental Medicine and Rheumatology department, QMUL (Registered as part of the Barts Health Human Tissue Resource Centre). These samples will be used to investigate markers of different types of cells, to better understand the mechanisms which lead to RA and potentially new treatment targets. The samples may also be used for future analysis in other projects which will have ethical approval. These samples will be considered as a gift to QMUL and will be stored securely by them indefinitely. If you decide to participate in this study, you agree to give/ "gift" your sample/s to the researchers who will then be able to use your sample/s for academic and/or commercial research purposes. You will not own the results generated using your sample/s, and you will not be entitled to any interest in or share of any profit that might arise from research using the sample/s.

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 (blood test) and before your injection (urine test) at no cost.

Tell one of the study doctors right away if:

- You are pregnant

- You get 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 participating in the trial.

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 study sponsor.

Will I be paid for taking part in this study?
You will receive a stipend for the time that is required to complete the study visits. You will receive the following amounts for each completed visit:

Visit 1: $ [Amount]
Visit 2: $ [Amount]
Visit 3: $ [Amount]
Visit 4: $ [Amount]
Visit 5: $ [Amount]

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
"Patient 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. [Site Name] 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 [Site Name] will be able to link the assigned

number to your name. 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
WIRB, 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 [Site Name]

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.

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 [Site Name]. 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 [Site Name]. There are no special procedures that must occur for you to withdraw from this study.

What other choices do I have if I do not participate in this study?
The alternative to participating is to not participate.

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, complaints, or if at any time you feel you have had a research-related injury or a reaction to the study drug, contact your study doctor:

[PI Name and Contact Information]

If you have questions about your rights as a research subject or have other questions, concerns, or complaints about the research, you can contact [IRB Name] at [IRB Phone Number]. A description of this clinical trial will be available at http://www.ClinicalTrials.gov, as required by U.S. Law. This website 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. A description of the trial will also be available on the EudraCT website, located at https://eudract.ema.europa.eu/.

In the event of an emergency, dial 911 (US) 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. [Last Name] if I have any more questions about taking part in this study. I understand that Dr. [LastName] 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)

_____