Subject Name: _____ **Date:** _____

Title of Study: ANK-mediated ATP efflux promotes CPPD deposition in cartilage: Study 1

Principal Investigator: Ann K. Rosenthal, M.D. **VAMC:** Milwaukee, WI

DESCRIPTION OF RESEARCH BY INVESTIGATOR:

You are being asked to participate in the research study entitled "ANK-mediated ATP efflux promotes CPPD deposition in cartilage." While the program will be under the supervision of Dr. Ann Rosenthal other professional persons may be designated to assist or act for her. Dr. Rosenthal receives financial support from the Department of Veterans Affairs to conduct this study and other research studies.

PURPOSE. The purpose of the study is to determine if a drug called probenecid can reduce quantities of adenosine triphosphate (ATP) in the joint fluid of people who have calcium pyrophosphate crystal deposition (CPPD) disease (also known as pseudogout). ATP has been shown to contribute to cartilage damage and calcium pyrophosphate crystal formation. Probenecid is approved by the Food and Drug Administration (FDA) to treat high levels of uric acid in the blood.

PROCEDURES. You are being asked to participate in this study because you have CPPD and have fluid in one or more of your joints. If you consent to participate, you will have a sample of fluid taken out of your joint on the first day. Removal of this fluid is part of standard care for your disease, but Dr. Rosenthal will use this fluid, which would normally be discarded, in this research study. You will be randomized (like the flip of a coin) to one of two groups:

Group 1 will receive their usual medications for CPPD. If you are in group 1, you will be asked to schedule a visit between six days and fifteen days from the day of your initial visits. You will receive regular phone calls from study staff for five days prior to your 2nd visit. At the 2nd visit you will return to the VA to have any remaining joint fluid removed . You will be offered a cortisone injection in the joint at that time and then followed for 3 days by daily phone calls. You may not be contacted by study staff on Saturday or Sunday, and if you finale phone call is scheduled on a weekend day, you will be contacted the following Monday.

Group 2 will receive their usual medications along with probenecid for five days prior to your 2nd visit. If you are in group 2, at the 2nd visit, the remainder of fluid will be removed from your joint and you will be offered a cortisone injection in your joint. You will also receive regular phone calls during the five days you take the medication and three days after you stop taking the medication to determine if you are having any side effects.

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You may not be contacted by study staff on Saturday or Sunday, and if you finale phone call is scheduled on a weekend day, you will be contacted the following Monday.

Standard treatment for CPPD includes cortisone injections as well as medications such as colchicine, prednisone and NSAIDs. The experimental aspect of this study is the use of probenecid and the two joint fluid aspirations (removal of joint fluid).

Tests and procedures done only for research purposes include the second joint aspiration and the use of probenecid.

Your participation will include seeing Dr. Rosenthal, having a sample of joint fluid drawn, being randomized to receive probenecid or no probenecid, and then returning between day 6 and day 15 to have joint fluid drawn again.

If you withdraw from the study early, you will be asked to let Dr. Rosenthal know. There are no consequences to withdrawing from the study early.

If you withdraw from the active treatment part of the study, you will be asked to complete the follow-up procedures outlined in this consent form. Information related to your participation in the study that was collected prior to termination of your participation may continue to be used and disclosed by the study doctor for the purposes described in this consent form. You can decide not to allow further information about you to be collected. If you decide this, you must inform your study doctor.

When your participation in the study ends, your doctor will discuss with you possible treatment options. These options include a corticosteroid injection into the joint.

Approximately 40 subjects will be involved in this study.

RISKS AND SIDE EFFECTS. As with any medical treatment, you may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors may not know all of the side effects that may happen. Side effects may be mild or very serious. Many go away soon after treatment is stopped, but in some cases, side effects can be serious, long-lasting, or permanent. A severe

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side effect may be life threatening. You should talk to your study doctor about any side effects that you have while taking part in the study.

The side effects that may occur as a result of participation in this study include bleeding or bruising around the site of joint aspiration. Infection after joint aspiration is extremely rare but can occur.

Probenecid is typically very well-tolerated, and because it is an older drug, its side effects are well-known. The side effects associated with probenecid are flushing, dizziness, fever, headache, rash, itching, hair loss, loss of appetite, nausea, sore gums, vomiting, blood in the urine or excess urination, low red cell counts (anemia) or low white blood cell counts, liver damage, rib pain, gouty arthritis, and kidney stones.

You may have an allergic reaction to this medication. As drug allergies can be severe or sometimes fatal, it is important to be aware of the signs and symptoms. If you have itching, shortness of breath, or swelling of the face, tongue, throat, or airway, you should seek medical attention immediately.

Any new findings discovered during the course of this project which may affect your willingness to continue participation will be provided to you. You will be asked to sign a new consent form to document that this new information has been explained to you.

Your participation in the study may be terminated by the investigator or sponsor without your consent if you do not follow instructions or if it is determined to be in your best interest.

PREGNANCY STATEMENT. If you are pregnant or become pregnant, the treatment/procedures that you are undertaking might involve risks to the embryo or fetus which are currently unforeseeable. Therefore, women who have the potential of becoming pregnant should use some form of effective birth control. Any female who is menstruating or is between the ages of 11 and 55 years with a uterus, tubes, and ovaries has the potential to conceive. Effective birth control is defined as the following: 1) Refraining from ALL acts of vaginal intercourse (abstinence); 2) consistent use of birth control pills; 3) injectable birth control methods (Depo-Provera, Norplant); 4) tubal sterilization or male partner who has undergone vasectomy; 5) placement of an IUD (intrauterine device); and 6) use, with every act of intercourse, of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam.

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COSTS TO SUBJECTS. It is possible that you may incur additional costs as a participant in this research study. You may be required to make additional trips to the Zablocki VAMC for clinic visits, procedures, or tests that would not be required if you were not a study participant.

Veteran or non-veteran subjects will not be required to pay for medical services received as a subject in an approved VA research study. Some veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study.

BENEFITS. The information that is obtained from this study may be useful scientifically and may possibly be helpful to others. Possible benefits to you include a reduction of ATP levels in your joint fluid, but this is not guaranteed.

ALTERNATIVE PROCEDURES. Your doctor will discuss appropriate alternative procedures with you. You may choose not to participate in the study and continue to receive your usual medications for the treatment of CPPD.

RESEARCH-RELATED INJURY. VA will provide medical care in the event you suffer a research-related injury associated with your participation in this study. You are, however, expected to comply with all prescribed study procedures. If you feel you have been injured as a result of participation in this investigation, you should contact Dr. Rosenthal at (414)384-2000, Ext. 41510. If you prefer, you may instead contact the Chief of Staff at (414)384-2000, Ext. 42600.

You have not released this institution from liability for negligence. Compensation may be payable, in the event of injury arising from such research, through a claim filed in accordance with the Federal Tort Claims Act. For further information, you may contact the Office of Regional Counsel at (414)902-5047.

CONFIDENTIALITY. Every effort will be made to maintain the confidentiality of your study records. Any information obtained from the research study that can be linked to you will be disclosed only as outlined in the attached Authorization for Release of Protected Health Information for Research Purposes form unless otherwise required by law. Any scientific data or medical information that results from the study may be presented at meetings and published so the information can be useful to others, but this data will not identify you. All research related records will be kept in secured and locked storage.

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Federal agencies including, but not limited to, the VA Office of Research Oversight (ORO) and the VA Office of the Inspector General (OIG), the Office for Human Research Protections (OHRP) of the Department of Health and Human Services, and the Government Accounting Office (GAO) may have access to records that identify you.

The Food and Drug Administration may choose to inspect research records that include your individual medical records. Subjects' names are not routinely required to be divulged to the FDA, but when they are, such information will be treated as confidential. However, on rare occasions, disclosure to third parties may be required. Therefore, absolute protection of confidentiality by the FDA is not promised or implied. By participating in this research project, you do not have the option of keeping your records from being reviewed by the FDA.

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.

SUBJECT STATEMENT:

RESEARCH SUBJECTS' RIGHTS. I have read or have had read to me all of the above. Dr./Mr./Ms._____ has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

I understand that participation in this study is voluntary, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw at any time without penalty or loss of VA or other benefits to which I am entitled. I was further informed that my decision about whether or not to participate will not prejudice my present or future relationship with the Zablocki VA Medical Center.

If at any time I have any questions, concerns, complaints, or input about the research, I may contact Dr. Ann Rosenthal at (414)384-2000, Ext. 41510 during the day and the VA operator can page Dr. Rosenthal at (414)384-2000 after hours. I understand that I may contact the Chairman of the Human Studies Subcommittee,

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the Associate Chief of Staff for Research, or the Research Subject Advocate at (414)384-2000, Ext. 41430 for further information related to my rights as a subject or to verify the validity of the study and authorized contacts. Information about VA research studies may be found at http://www.ClinicalTrials.gov.

By my consent to participate in this research study, I authorize the use of my bodily fluids, substances, or tissues for study purposes as indicated above.

If I wish to withdraw from the study, I will notify Dr. Rosenthal at (414)384-2000, Ext. 41510.

Department of Veterans Affairs	**VA RESEARCH CONSENT FORM** (Page 7 of 7)

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I have been informed about my rights as a research subject, and I voluntarily consent to participate in this study. I have been told what the study is about and how and why it is being done. I will be given a signed copy of this consent form.

_____ _____

Signature of Subject Date Time (optional)

If applicable: by VA policy, when subject is unable to sign or a mark such as an "x" is utilized TWO signatures are required to witness the signing of this document

_____ _____ _____

Signature of Witness Date Name of Witness (print)

_____ _____ _____

Signature of Witness Date Name of Witness (print)

I have fully explained the study as described to the subject, and answered all their questions. I attest that this subject gave written, informed consent before any research related procedures began.

_____ _____

Signature of Person Authorized to Obtain Consent Date

_____

Name and Position Title (print)

FILE A SIGNED COPY OF THIS CONSENT IN THE SUBJECT'S MEDICAL RECORDS if so required.
The ORIGINAL must stay with the investigator's research records.
Pharmacy and others may require signed copies. Subject MUST also receive a signed copy.