Northwestern University
Consent Form and HIPAA Authorization for Research

PROTOCOL TITLE: EFFECTS OF NICOTINAMIDE AND LANTHANUM CARBONATE ON SERUM PHOSPHORUS AND FGF23 LEVELS IN PATIENTS WITH STAGE 3-4 CHRONIC KIDNEY DISEASE

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SUPPORTED BY: The National Institutes of Health (NIH)

Introduction

You are being asked to take part in a research study. This document has important information about the reason for the study, what you will do if you choose to be in this research study, and the way we would like to use information about you and your health.

Conflict of interest disclosure

The following disclosure is made to give you an opportunity to decide if this relationship will affect your willingness to participate in this research study:

If your doctor is also the person responsible for this research study, please note that he/she is interested in both your clinical care and the conduct of this research study. You have the right to discuss this study with another person who is not part of the research team before making your decision whether or not to be in the study.

What is the reason for doing this study?

Myles Wolf, MD, MMSc, is conducting a research study sponsored by the National Institutes of Health to determine new methods to lower serum phosphorus levels and levels of the hormone "FGF23"(Fibroblast Growth Factor 23) in chronic kidney disease patients.

You are being asked to participate in this research study because you have chronic kidney disease, a condition in which your kidneys do not filter substances from the blood as well as healthy kidneys.

Phosphorus is a mineral found in many foods. It works with calcium and vitamin D to keep bones healthy. Healthy kidneys keep the right balance of phosphorus in the body. FGF23 is a hormone that helps the kidneys to control the blood levels of phosphorus. Hormones are natural substances, made by the body and measured in the blood, that affect various bodily functions. FGF23 “tells” the kidneys how much phosphorus to get rid of in the urine.

In people with chronic kidney disease, kidneys struggle to get rid of enough phosphorus, so FGF23 levels increase in the blood to help get rid of extra phosphorus. Over time, with progressive loss of kidney function, both phosphorus and FGF23 can build up in the blood simultaneously. Researchers believe that too much phosphorus and FGF23 in the blood may

lead to weak bones that break easily, increase the risk of heart problems, and accelerate progression of kidney disease. However, the best way to control phosphorus and FGF23 levels in the blood in patients with chronic kidney disease is not known.

The purpose of this research study is to:

- test the effectiveness of the study drugs, nicotinamide and lanthanum carbonate, either individually or in combination, to lower blood levels of phosphorus and FGF23;
- determine the tolerability and safety of the study drugs, nicotinamide and lanthanum carbonate, either individually or in combination over 12 months in patients with chronic kidney disease;
- test the effects of the study drugs on bone, heart and kidney health.

This is a research study to test two drugs being used for investigational purposes. Each study drug is described in more detail below.

Nicotinamide (also called niacinamide or Vitamin B3) is a water soluble vitamin that is essential to health at low doses for all individuals. Nicotinamide is not regulated by the United States Food and Drug Administration (FDA), but is marketed and distributed as a dietary supplement in the United States. Studies in animals show that nicotinamide at higher doses limits the amount of phosphorus absorbed by the intestine from food into the blood. Nicotinamide has also been tested in small studies of dialysis patients (patients with complete loss of kidney function), and was associated with substantial reductions in blood phosphorus levels. Prior large-scale studies have tested high doses of nicotinamide in healthy individuals who took the medicine for up to 5 years. In these studies, nicotinamide was found to be safe and well tolerated. The rate of side effects in participants who took nicotinamide was comparable to the rate in participants that received placebo. (A placebo is an inactive substance that is made to look like the study drug.)

Lanthanum carbonate (also called Fosrenol) is a phosphorus binding medication that is used in patients on dialysis to reduce the amount of phosphorus that the body is able to absorb from the diet. These tablets are used when blood levels of phosphorus are too high. Fosrenol is approved by the FDA to treat high phosphorus levels in the blood of patients on dialysis, but has not been approved by the FDA for people with chronic kidney disease not severe enough to require dialysis.

This study also uses a placebo. A placebo looks like the study drug, but contains no active medication. Placebos are used in research studies to learn if helpful or harmful effects seen in research participants are truly from the study drug. If you take part in this study, you will have a 1 in 2 (50%) chance of getting placebo, and a 1 out of 2 (50%) chance of receiving the active drug for **each** of the two medications used.

Because this is a research study, the nicotinamide and lanthanum carbonate will be given to you **only** during this study and not after the study is over.

We will obtain Magnetic Resonance Imaging (MRI) scans (no injection of dye (contrast)) of heart and kidneys to answer our research questions. There are no known radiation risks associated with MRI, and the images we will obtain in this study do not require contrast.

Cardiac MRI uses structural MRI to look at the heart. Cardiac MRI is a type of scan that uses magnetic fields and radio waves to make a picture of the size of the chambers of the heart.

Renal MRI uses blood oxygenation level dependent (BOLD) functional MRI to look at the kidneys. BOLD MRI is a type of scan that uses magnetic fields and radio waves to make a picture of kidney function.

Additional information regarding these procedures will be provided below. If you decide not to have the MRI scans or if we determine that you should not have them, you can proceed with the other study procedures.

If we determine that it is safe for you to receive MRI scans and if you choose to have them, then the following procedures will take place during your MRI scans.

The MRI scans will take place at the Olson Pavilion, 710 North Fairbanks, Basement, Chicago, IL. Each MRI study visit will take about 1.5 hours. On the days of the MRI visits, you will come after fasting for at least 4 hours. Fasting refers to food and drinks only; you should take your medications without interruption. If you take insulin, your study doctor /staff will tell you what to do about taking it on the day of the MRI.

At these visits we will:

- Take a cardiac MRI scan (no contrast) to check size of the chambers of your heart;
- Take a renal MRI scan (no contrast) to check the function of your kidneys.

You will have one cardiac and one renal MRI scan (no contrast) when you start the study. These will be repeated 12 months later.

How many people will take part in this study?

The study investigators hope to enroll 50 subjects at Northwestern University and 200 nationwide. The study sites are Northwestern University, North Shore University Health System, George Washington University, University of California San Diego, Denver Nephrology and University of Utah.

What will you do if you choose to be in this study?

If you consent to participate, your participation in this study will last approximately **12** months and include **11** study visits. The study visits will take place at the Center for Translational Metabolism and Health located at633 N. St. Clair, , 18th floor.. The following tests and procedures will be performed to determine if you qualify to take part in this study during the screening visit:

Screening Visit
This study visit will last approximately 1 hour. During this visit you will meet with a member of the research team who will explain the study in detail to you. You will be asked to read this consent form carefully. If you would like to participate, we will ask you to sign the consent form. You will get a signed copy to keep for your records.

After you sign the consent form, we will do some tests and procedures to see if you qualify to take part in this research study. A member of the research team will review the results of these tests and procedures. If you don't qualify, we will tell you why. The following procedures will be done:

- We will measure your blood pressure, heart rate, height and weight.
- We will ask you questions about your medical history and current medications.
- We will ask you additional questions to find out if it is safe for you to have the MRI scans.
- About 3 tablespoons (45 mL) of blood will be drawn. We will measure your electrolytes, BUN/creatinine (a measure of kidney function), parathyroid hormone, serum phosphorus, serum glucose, total blood count, LFT (liver function test), and CK (creatine kinase, a muscle function test).
- We will do a urine pregnancy test if you are a woman under 50 years old.

You will not be able to participate in the study if we find that your:

- blood count is too low
- platelet count is too low (platelets help to control blood clotting)
- albumin level is too low (albumin is a protein in the blood)
- liver function tests are high
- levels of parathyroid hormone in your blood are too high (parathyroid hormone controls how calcium is used in the body)
- levels of phosphorus in your blood are too low
- levels of CK in your blood are too high (Creatine Kinase (CK) is a muscle enzyme)
- urine pregnancy test is positive or if you are breastfeeding a child
- you eat less than 2 meals per day

If you qualify for the study, you will proceed into the Baseline Period, described below.

Baseline Period (Baseline Visits 0, 1 and 2)
The Baseline Period will include a run-in (time on study before you receive the study treatment) that will last 3 weeks and will consist of three visits. During this time the research team will evaluate how well you do with the study procedures. You will be asked to collect all of your urine over 24 hours at home on two separate occasions and to return these samples to the study personnel. You will also receive information about how to keep a low phosphorus diet. During this time, you will also receive an MRI scan (no contrast) of your heart and kidneys. Your MRI scan (no contrast) visit could coincide with one of the Baseline visits, or it could take place on a different day.

Baseline Visit 0 will take approximately 30 minutes to complete. At this visit, the following procedures will be performed:

- We will give you a container for 24-hour urine collection and instructions. We will ask you to return the 24 hour urine specimen at your next study visit.
- We will ask you to complete a questionnaire about gastrointestinal (stomach) symptoms you may be having. This questionnaire should take less than 5 minutes to complete.
- We will give you study medications, which you will be asked to start taking according to instructions. To help us count how many tablets you have taken, we will ask you to bring the study pill bottle back with you to your next visit.

Baseline Visit 1 will take approximately 1 hour to complete. At this visit, the following procedures will be performed:

- You will be asked to deliver your first 24-hour urine collection to study personnel. This sample will be used to measure 24-hour urine phosphorus, calcium, and to determine your kidney function, creatinine and urea nitrogen (BUN).
- We will check your blood pressure, heart rate, and weight.
- About 4 tablespoons (60 mL) of blood will be drawn to measure FGF23, uric acid, hemoglobin A1c (a marker of glucose control/diabetes), electrolytes, BUN, creatinine, glucose, albumin, parathyroid hormone, calcium, and phosphorus levels.
- If you agree, we will draw blood samples (30 mL, 2 tablespoons) and save urine samples to store for future studies (refer to the **Optional Study Elements** section at the end of this form).
- We will ask you for a urine sample. This sample will be used to test urine phosphorus, calcium, albumin, and creatinine. This sample will not require a timed collection, but will be a "spot" specimen provided at the time of your visit.
- We will give you a container for your second 24-hour urine collection and instructions. We will ask you to return the 24-hour urine specimen at your next study visit.
- You will be asked to bring in your study medication pill bottle with you, so we can count how many tablets you have taken.
- A member of the research team will review with you information about keeping a low phosphorus diet and will instruct you on how to avoid food items high in phosphorus.
- We will give you a questionnaire to fill out about any gastrointestinal (stomach) symptoms you may have, about your ability to take the study drugs, and to assess for any potential side effects of the study drugs.

Baseline Visit 2 will take approximately 1 hour to complete. At this visit, the following procedures will be performed:

- You will be asked to deliver your second 24-hour urine collection to study personnel. This sample will be used to measure 24-hour urine phosphorus, creatinine, calcium, and urea nitrogen.
- We will check your blood pressure, heart rate, and weight.
- We will draw a blood sample of approximately 3 tablespoons (45 mL) to measure your FGF23, serum phosphorus, electrolytes, BUN/creatinine (a measure of kidney function), glucose, parathyroid hormone, and calcium levels.
- If you agree, we will draw blood samples (30 mL, 2 tablespoons) and save urine samples to store for future studies (refer to the **Optional Study Elements** section at the end of this form).

- We will ask you for a "spot" urine sample. This sample will be used to test the urine for phosphorus, calcium, albumin, and creatinine.
- A member of the research team will review with you information about keeping a low phosphorus diet and will instruct you on how to avoid food items high in phosphorus.
- You will be asked to bring in your study medication pill bottle so we can count how many tablets you have taken.
- We will give you a questionnaire to fill out about any gastrointestinal (stomach) symptoms that you may have, about your ability to take the study drugs, and to assess for any potential side effects of the study drugs.
- You will be randomized into 1 of 4 groups (see **Randomization to Study Groups** section below).
- You will receive a 30-day supply of study drugs based on the study group you are randomized to.

Cardiac MRI procedures

For the cardiac MRI Scan (no contrast), we will:

- We will ask you to complete an MRI safety questionnaire before you receive your MRI.
- We will ask you to change into a hospital gown and remove any jewelry/bra/metal objects.
- We will ask you to lie very still on the scanning table.
- We will attach ECG (electrocardiogram) electrodes to you, as the pictures are taken in time with your heartbeat.
- We will place a lightweight pad with a scanning device (radio antenna) over your chest.
- We will give you a squeeze ball that you can squeeze to stop the MRI scan if you feel you need to.
- We will place you inside the MRI scanner with a set of headphones or ear plugs.
- You will remain in communication with the MRI technician when in the MRI scanner.
- You may hear a loud knocking sound during the MRI scan, which indicates that a picture is being taken. During this time you should breathe quietly and remain still. For some scans you may be asked to hold your breath for up to 20 seconds.

The scan will take about 30 minutes.

Renal MRI procedures

For the renal MRI Scan (no contrast):

- We will reposition the scanning device (radio antenna) over the abdomen.
- We will give you a squeeze ball that you can squeeze to stop the MRI scan if you feel you need to.
- We will place you inside the MRI scanner with a set of headphones or earplugs.
- You will remain in communication with the MRI technician when in the MRI scanner.
- You may hear a loud knocking sound during the MRI scan, which indicates that a picture is being taken. During this time you should breathe quietly and remain still. For some scans you may be asked to hold your breath for up to 20 seconds.
- We will put in an intravenous line ("IV") in your arm. An IV is a thin, flexible plastic tube that is threaded into a vein using a needle. It allows us to inject medications into your vein
- We will inject 20 mg of Furosemide (Lasix, a drug used to get excess water out of the body and increase urine; "water pill") into your vein, and we will take more pictures.

The scan will take about 30 minutes.

The total duration of the MRI study visits will be approximately 1.5 hours.

Randomization to Study Groups
This is a randomized, double-blinded study, which means that neither you or the study doctor or the study staff will know which treatment you are receiving. However, in an emergency, study doctors can get this information. Randomization means you will be randomly assigned to a treatment based on chance, like a flip of a coin. Neither you nor the researcher chooses your assigned group. You will have an equal chance of being in any one of the four groups.

At the end of Baseline Visit 2, we will review your results from Baseline Visit 1 and determine if you still qualify for the study. If you don't qualify, we will tell you why.

If you remain eligible for the study, you will be randomly assigned to 1 of 4 groups:

- First group: Will receive both nicotinamide and lanthanum carbonate,
- Second group: Will receive lanthanum carbonate and nicotinamide placebo,
- Third group: Will receive lanthanum carbonate placebo and nicotinamide,
- Fourth group: Will receive lanthanum carbonate placebo and nicotinamide placebo.

Taking the Study Drugs
At every follow up visit, we will give you a supply of study drugs to take home with you.

You will chew one 500 mg lanthanum carbonate (or placebo) tablet three times a day with meals for the first month on the study. Thereafter, from months 2 through 12, you will chew two 500 mg lanthanum carbonate (or placebo) tablets three times a day with meals, unless instructed otherwise by study staff.

You will take one 750 mg nicotinamide tablet (or placebo) by mouth once per day for the first month on the study. Thereafter, from months 2 through 12, you will take one 750 mg nicotinamide tablet (or placebo) by mouth twice a day, unless instructed otherwise by study staff.

It is important for you to follow our instructions about how to take the study drugs. Bring any unused study drugs or your empty pill bottles with you to your next study visit.

Doses or frequency of your study medications may need to be adjusted during the study and members of the study team will give you detailed instructions on any changes.

Follow up Period (Follow up Visits 1-12)
During this period, you will make 7 additional visits, which will be a month apart during the first 3 months and thereafter the visits will be 3 months apart for 2 additional visits, and then at a 2 month and 1 month follow-up interval during the last 3 months of the study. The visit names correspond to the month of the follow up period. For example, follow up visit 6 corresponds to

the 6th month of follow up. At the end of the follow up period, you will have your final cardiac and renal MRI scans (no contrast).

During Follow up Visits 1-9 and 12, the following procedures will be done:
- We will ask you questions about your current health and medications you are taking.
- We will draw blood samples (about 4 tablespoons (60 mL)) to measure your FGF23, phosphorus, electrolytes, glucose, and BUN/creatinine (a measure of kidney function).
- We will measure PTH and calcium levels during **Follow up Visits 3, 6, 9 and 12.**
- We will measure uric acid and HbA1C (an average measure of blood sugar) levels during **Follow up Visits 6 and 12.**
- We will also draw lab tests, including CBC (blood count), LFT (liver function test) and CK/creatinine kinase (muscle function test), to monitor your treatments for safety. In the event that these show abnormalities, they may trigger additional visits.
- A member of the research team will review with you information about a low phosphorus diet and will instruct you on how to avoid food items high in phosphorus.
- You will be asked to bring in your study medication pill bottles with you at each study visit so that we can count how many tablets you have taken.
- We will give you a questionnaire to fill out about any gastrointestinal (stomach) symptoms that you may have, about your ability to take the study drugs, and about any side effects from the study drug.

During Follow up Visits 3, 6 and 12, if you agree, we will draw blood samples (30 mL, 2 tablespoons) and save urine samples to store for future studies (refer to the **Optional Study Elements** section at the end of this form).

During Follow up Visits 2, 3 and 11, the following additional procedures will be done:
- We will give you a container for your 24-hour urine collection and instructions so we can measure the amount of phosphorus, calcium, creatinine, and urea nitrogen you are excreting in your urine.
- You will be asked to return your 24-hour urine collections at **Follow up Visits 3, 6 and 12**. This sample will be used to measure 24-hour urine phosphorus, creatinine, calcium, and urea nitrogen tests.

During Follow up Visit 9, the following additional procedures will be done:
- We will check your blood pressure, heart rate, and weight.

During Follow up Visits 3, 6, and 12, the following additional procedures will be done:
- We will check your blood pressure, heart rate, and weight.
- We will ask you for a "spot" (untimed) urine sample. This sample will be used to conduct spot urine phosphorus, calcium, albumin, and creatinine measurements.

At the end of the follow up period, you will have your final cardiac and renal MRI scans (no contrast). The procedures for these tests will be the same as during the Baseline Period. If you leave the study early, we may ask you to do these scans in advance of the 12th month.

Unscheduled visits
In addition to the follow up visits described above, you may be asked to come back for additional unscheduled visits during which the following procedure will be done.

- If the study physician thinks you need additional blood testing, we will draw a blood sample to monitor your treatments for safety.
- You will bring in your study medication pill bottles with you; so that we can count how many tablets you have taken.
- We will give you a questionnaire to fill out about any gastrointestinal symptoms that you may have, about your ability to take the study drugs, and about any side effects from the study drugs.
- The doses or frequency of your study medications may be adjusted.

Telephone calls
In addition to the scheduled follow up visits and unscheduled visits, a member of the study team may contact you by phone between your visits to determine how you are feeling and whether or not doses or frequency of your study medications need to be adjusted. You may also be asked if you are having any trouble taking any of your study medications, and if you have been started on any new medications since the last visit. Information obtained during the telephone calls may trigger an unscheduled visit to ensure your safety while taking the study medications.

Taking Other Medications During the Study
During the 12 months duration of the study, you will be asked not to take any non-study medicine that binds phosphorus. These include Tums©, calcium carbonate, sevelamer carbonate or Renvela©, calcium acetate or Phoslo©. You will be asked not to take over the counter forms of nicotinamide, though a standard multi-vitamin can be taken. If your non-study doctor feels that these medications are necessary, you will be taken off of the study drugs but we will ask you to continue to make follow up visits until study completion. You will be asked not to take activated forms of vitamin D such as calcitriol, paracalcitol or Zemplar©, doxercalciferol or Hecterol©.

After You Complete the Study
After you complete the study, we will refer you back to your own doctor for your ongoing medical care.

All procedures conducted for this study are for research purposes only.

<u>What are some of the possible risks and discomforts?</u>
Risks of hypophosphatemia (low phosphorus levels in the blood).
Severe hypophosphatemia (very low phosphorus levels in the blood) can cause muscle weakness, muscle cramps and shortness of breath. Other very rare (less than 0.01% chance) side effects of severe hypophosphatemia include: irritability, paresthesias (feeling of pins and needles), confusion, seizures, coma, heart failure, muscle breakdown, low platelet count, which leads to bleeding and rarely anemia and reduced function of white blood cells that fight infection. Prior studies using lanthanum carbonate and nicotinamide individually in persons with chronic kidney disease produced only very mild decreases in blood phosphorus levels. We do not expect your phosphorus levels to decrease to dangerous levels. A small decrease will not cause any

symptoms, and researchers believe that small decreases may be beneficial to health. Your phosphorus levels will be checked repeatedly throughout the study when blood and urine samples are collected. If the phosphorus levels are found to be too low you will be notified by the study team and asked to return for an unscheduled visit for repeat blood draw to verify the blood phosphorus level. If low levels are confirmed, we will decrease the dose of lanthanum carbonate by half and reduce the frequency of nicotinamide from twice a day to once a day and repeat the lab tests. If the level of phosphorus remains too low, we will stop both study drugs and repeat the lab tests. Once the low phosphorus level is resolved, study drugs will be reintroduced at reduced doses and safety assessments will be done during follow up visits.

You may have side effects from the specific study medications, as described below.

Lanthanum carbonate
Lanthanum carbonate may cause nausea, vomiting, diarrhea, or abdominal pain. It must be taken **with** meals to reduce the likelihood (1-10% chance) of developing these side effects. You will be asked about these side effects during your study visits. You can also contact us at any time if you experience any of these symptoms. If you develop any of these side effects we will decrease the dose of lanthanum carbonate by half. If you still cannot tolerate the medicine on the lower dose, we will stop the study drug.

Nicotinamide
In patients receiving dialysis, nicotinamide has rarely been associated with low blood platelet counts. Blood platelets help stop bleeding, and low levels may predispose to bruising and bleeding risk. In these studies, the platelet counts returned to normal quickly after holding the study drug. This is not a recognized side effect of nicotinamide use in other settings, and based on the body's handling of nicotinamide in people with less severe kidney disease, we do not anticipate low platelet counts or bleeding in this trial (less than 1% chance). Nonetheless, we will monitor closely for this possibility with frequent blood tests. For safety, the study medication will be held if your blood platelet count drops below a safety threshold.

Nicotinamide has some similarities to the cholesterol lowering medicine niacin. Niacin commonly causes flushing, often experienced as an intense hot flash shortly after consumption. Niacin has also been known to increase the risk for gout, cause muscle injury, and worsen glucose control (less than 5% chance). Prior studies suggest that these effects are largely due to the **non-nicotinamide** components within niacin. Nonetheless, we will monitor you with serial blood tests for uric acid (a marker for gout risk), muscle injury, and glucose control. For safety, the study medication will be held if your markers of muscle injury increase above a safety threshold.

Niacin and nicotinamide may also alter liver function tests. Liver injury is reported to be rare with nicotinamide, but we do not know if it is more common in people with kidney disease. We will monitor you with serial blood tests for liver function. We will also ask you to report to us and your doctor the following symptoms that may be related to liver disease: nausea, vomiting, abdominal pain, yellowing of the skin, and itching. For safety, the study medication will be stopped if your liver blood tests increase above a safety threshold.

Nicotinamide may cause dyspepsia (upset stomach), heartburn, and bloating in some cases (1-10% chance). We will monitor for these symptoms using questionnaires at each visit.

In dialysis patients, high dose nicotinamide has been associated with diarrhea in some cases (less than 5% chance). We will monitor these symptoms using questionnaires at each visit.

You will be asked about these side effects during your study visits. You can also contact us at any time if you experience any of these symptoms. If you develop any of these side effects we will decrease the frequency dosing of nicotinamide. If you still cannot tolerate the medicine with the lower frequency, we will stop the study drug.

Risks of the study procedures:

Blood Draws

Blood drawing may cause a small amount of pain. In addition, a temporary bruise or "black and blue mark" may develop. Rarely, people faint after having blood drawn. Very rarely, the vein may become inflamed (swollen, sore) or infected at the place where blood was drawn, which can be treated.

24 hour-urine collection

The collection of all urine for 24 hours of urine may be cumbersome.

Study questionnaires

Participating in this research may involve providing details that you consider confidential or private. Some of the questions may make you upset or uncomfortable. You have the right to refuse to answer any of the questions.

MRI scans

MRIs use powerful magnets to make images. There are no known radiation risks associated with MRI, and the images we will obtain in this study do not require contrast. Some people cannot have an MRI because they have some type of metal in their body. For instance, if you have a heart pacemaker, artificial heart valves, metal implants such as metal ear implants, bullet pieces, chemotherapy or insulin pumps or any other metal such as metal clips or rings, you should not have an MRI. During this test, you will lie in a small closed area inside a large magnetic tube. Some people are scared or anxious in small places (claustrophobic). The MRI scanner makes loud banging noises while taking a measurement, so either ear plugs or specially designed headphones will be used to reduce the noise. The MRI can be stopped at any time at your request.

We are doing the MRI in this study to answer research questions and not for medical care purposes. The information created by this study will not become part of your hospital record. These MRI scans are not the same as the ones that your own doctor would order. It may or may not show problems that would be found in standard MRIs. If we do see something that looks like a medical problem, we will ask a radiologist (a doctor who specializes in reading these kinds of scans) to look at the results. If the radiologist thinks there might be a problem, we will tell

you and help you get follow-up care. If the radiologist thinks that you might have a medical problem, but it turns out that you don't, we may have caused you to worry for no reason.

IV placement

An IV may cause a bruise and/or bleeding at the needle site. Depending on the length of time the IV is in place, a bruise may last for a day or so. Occasionally a person feels faint when blood is drawn. Rarely an infection may develop. If infection does occur, it can be treated.

Furosemide (Lasix)

Furosemide may increase your urine production and lower your potassium levels and blood pressure. Other very rare side effects of furosemide include upset stomach, dizziness, rash, sensitivity to light, and ringing or buzzing noises in the ears. You will receive a single dose of furosemide. At this dose, your potassium levels and blood pressure will most likely stay the same. The other side effects are also extremely rare after a single dose of furosemide.

Fasting for 4 hours prior to MRI

We will ask you to fast at least 4 hours prior to the MRI visits. There is a risk for low blood sugar when you fast. If you are taking insulin, we will ask you to take one half of your morning dose of insulin. We will also remind you to eat a snack after completing the MRI test. This will help prevent a risk of a hypoglycemic event.

Unknown Risks

There may be other side effects, in addition to those described here, that are not known at this time. We will give you any new information that we learn during the course of the study. This new information might affect your willingness to be in or stay in the study. If you notice any side effects during the study, you should tell us right away.

Unforeseeable risks

Because this is an investigational study there may be some unknown risks that are currently unforeseeable. You will be informed if the researchers learn of any change in the amount of risk to you.

What do I need to know about reproductive health/sexual activity if I am in this study?

The effect of the study drug on pregnancy and breast feeding is uncertain. Therefore, women who are pregnant, may become pregnant, or are breastfeeding, will be excluded from this study. **If you become pregnant, or think you may be pregnant during the study, you should notify the study staff immediately.**

If sexually active, women should use an effective method of birth control while taking the study drug. Barrier contraceptives (condoms or diaphragm) with spermicide, intrauterine devices (IUD's), hormonal contraceptives, oral contraceptive pills, surgical sterilization, and complete abstinence are examples of effective methods.

If you are considered to be postmenopausal, you are not required to use contraception while in this study. Rarely, women considered to be postmenopausal become pregnant. If you suspect that you become pregnant while taking the study drug, it is important that you tell the study nurse/doctor immediately.

What are the possible benefits for me or others?

You are not likely to have any direct benefit from being in this research study. Results from this study may benefit other people with kidney disease in the future.

What other procedures or courses of treatment might be available to me?

You do not have to be in this study to receive treatment for your kidney disease**.**
This research study is for research purposes only. The only alternative is to not participate in this study. High phosphorus levels are uncommon in patients with chronic kidney disease who are not yet on dialysis. Use of phosphorus binders in this population when serum phosphorus levels are within the normal range is not recommended. For these reasons, most likely you would not receive any treatment outside this study for your phosphorus levels. However, if you have additional questions, you should discuss participation in this study with your doctors.

Are there any financial costs to being in this study*?*

There will be no costs to you for being in this study. There will be no costs to you or your insurance for any procedures or testing done only as part of this research study. If you receive a bill for services that you think could be related to your participation in this study, you should contact the study physician.

Travel Expenses:

You will be given reimbursement for expenses related to parking, bus or train fare. You will need to provide receipts for travel expenses.

Will I receive payment for participation in this study?

You will receive $50 payment for participating in the screening visit. If you are deemed eligible to participate, you will receive $50 for each completed study visit. The protocol contains 11 study visits. If you complete all study visits your total compensation will be $550. If you participate in the MRI component of the study, for each MRI visit you will receive an additional $225 for a total of an additional $450. Therefore, if you complete all the study visits and receive the MRI scans at the beginning and end of study, you will receive $1000. You will be paid by check from the accounting services at Northwestern University following each study visit. If you withdraw from the study, you will be paid for the portions that you completed. You will not receive any payment for any unscheduled visits (however, transportation to the clinic will be reimbursed).

The Accounting Services at Northwestern University will be given your name, address, and Social Security Number in order to issue a check for your study participation. Study payments are considered taxable income and reportable to the IRS. A Form 1099 will be sent to you if your total payments are $600 or more in a calendar year.

What should I do if I am injured as a result of being in this study?
If you become ill or get an injury or illness as a result of study (medications, devices or procedures), you should seek medical treatment through your doctor or treatment center of choice. You should promptly tell the study doctor about any illness or injury.

The Northwestern University researchers will not pay for medical care required because of a bad outcome resulting from your participation in this research study. This does not keep you from seeking to be paid back for care required because of a bad outcome.

If I have questions or concerns about this research study, whom can I call?
You can call us with your questions or concerns.

If you have any illness or injury during your time on this study, you should call us promptly. Dr. Myles Wolf and Dr. Tamara Isakova are the researchers in charge of this study. You can call them at 312-503-6921 during office hours Monday through Friday from 8am to 5pm.

You can also call study coordinators Michelle Bradley at 312-503-1909, Gina Schwartz at 312-503-3865, Patrick Fox at 312-503-1887, or Carlos Martinez at 312-503-1808 with questions about this research study during office hours Monday through Friday from 8am to 5pm.

For problems arising evenings or weekends, you may call the Northwestern Memorial Hospital operator at 312-926-2000 and ask to have Dr. Myles Wolf or Dr. Tamara Isakova paged.

What are my rights as a research subject?
If you choose to be in this study, you have the right to be treated with respect, including respect for your decision whether or not you wish to continue or stop being in the study. You are free to choose to stop being in the study at any time.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. Specifically, your choice not to be in this study will not negatively affect your right to any present or future medical treatment.

Any new findings developed during the course of this research that may affect your willingness to continue in this study will be shared with you.

Your participation in this study may be stopped by the investigator without your consent for the following reasons:

- If it appears to be medically harmful to you;
- If you fail to follow directions for participating in the study;
- If it is discovered that you do not meet the study requirements;
- If the study is canceled; or
- For administrative reasons, including competitive enrollment - the target number of subjects has entered the treatment phase.

If you want to speak with someone who is not directly involved in this research, or have questions about your rights as a research subject, please contact the Northwestern University Institutional Review Board (IRB) Office. You can call them at 312-503-9338.

What about my confidentiality and privacy rights?

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Your health information we may collect and use for this research includes:

- All information in a medical record
- Results of physical examinations
- Medical history
- Lab tests, or certain health information indicating or relating to a particular condition as well diaries and questionnaires
- Records about study medication or drugs

Participation in this study requires collecting private data about you including your social security number (in order to issue a check for your study participation), contact phone number and email and contact information for someone close to you. This personal health information will provide a mechanism for us to contact you for safety reasons, for example if we observe an unexpected finding on your blood or urine tests that require follow-up or a change in therapy. You will be assigned a unique study ID that bears no relation to your personal health information. This is a multi-center study, other patients will be recruited at other institutions across the US. Data from all sites will be combined for data analysis. The study has a Data Coordinating Center at the Cleveland Clinic. To protect your privacy, when your data are sent to the Cleveland Clinic Data Coordinating Center, only your unique study ID will be used. The study database at the Cleveland Clinic will not include your name, address, phone number, or other personal health information.

Your research records will be labeled with a unique study ID. The list that matches your name with the study ID will be kept in a locked file in the research team's office. Any research records that identify you will be kept only as paper records in a secure location, or as files behind a secure computer firewall.

Your blood and urine samples will be labeled only with the study ID number, the date of collection, and the study visit number.

A final dataset will be developed using your data and data from other participants in this study. This dataset will not contain your personal health identifiers, but only your unique study ID number. The de-identified dataset will be maintained for data analysis through December 31, 2033.

Any presentations or publications from this information will not identify you.

The following groups of people may give the researchers information about you:

- All current and previous health care providers, including but not limited to Northwestern Medical Group (NMG) and Northwestern Memorial Hospital (NMH).

Once we have the health information listed above, we may share some of this information with the following people. Please note that any research information shared with people outside of Northwestern University and its clinical partners (or affiliates) will not contain your name, address, telephone or social security number or any other direct personal identifier unless disclosure of the direct identifier is required by law [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigators office]

- Authorized members of the Northwestern University workforce, who may need to see your information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board (a committee which is responsible for the ethical oversight of the study).

    - Clinical affiliates, including but not limited to Northwestern Medical Group (NMG) and Northwestern Memorial Hospital (NMH). Your participation in this clinical trial will be tracked in an electronic database and may be seen by investigators running other trials that you are enrolled in and by your healthcare providers

    - Clinical affiliates, including but not limited to Northwestern Medical Group (NMG) and Northwestern Memorial Hospital (NMH), for purposes including, but not limited to, the affiliate's provision of care to you and/or the affiliate's scheduling of appointments and/or billing activities.

- Other University research centers and University contractors who are also working on the study.

- Study monitors and auditors who make sure that the study is being done properly.

- Government agencies and public health authorities, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS).

- Registries or other research-related databases: The study data will be submitted to the NIDDK Data Repository. The data repository will keep the data de-identified (without your personal identifying information) from this NIH study available to future researchers forever.

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission.

The results of this study may also be used for teaching, publications, or presentations at scientific meetings. Any presentations or publications will not identify you.

ClinicalTrials.gov

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.

Please note that:

- You do not have to sign this consent form. If you do not, it will not affect your treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits. However, you will not be allowed to take part in this research study.
- You may change your mind and "take back" (revoke) this consent at any time. Even if you revoke this consent, the Principal Investigator may still use or share health information that was obtained about you before you revoked your consent as needed for the purpose of this study. To revoke your consent for the use of your health information, you must do so in writing to:

  PI's Name: Myles Wolf, MD

  Institution: Northwestern University

  Department: Institute of Public Health and Medicine

  Address: 633 N. St Clair, Suite 18-089
- Unless you revoke your consent, it will not expire.
- If you agree to have your sample(s) stored in the Repository, you can change your mind up until the end of the COMBINE study. When study researchers receive written instructions from you, they will destroy your sample and all information that identifies you. After the COMBINE study ends, you will not be able to withdraw your sample because the Repository will not know which one is yours. The sample will stay in the Repository indefinitely.

Optional Study Elements:

Future Use of Data: After completion of the trial, a copy of the de-identified data will be retained for future research. The dataset will not contain any data that will identify you, but rather only your unique study ID. De-identified data may be shared with associates of the study investigators, pending approval by the institutional review board, and kept in a locked file in the research team's office. Any research records that identify you will be kept only as paper records in a secure location, or as files behind the secure computer firewall.

Data linking your personal health identifies with the unique study ID codes in the dataset will be retained only by the study physician. These files will allow linkage with administrative datasets

such as Medicare claims data to determine long-term outcomes such as death and dialysis initiation. In all cases, data will be kept in a locked file in the research team's office.

Blood and urine samples stored for future research

Allowing for the storage and future testing of your tissue and blood samples will involve no cost to you.

The primary purpose of the blood and urine specimens that you will provide is (1) to determine the effects of nicotinamide and lanthanum carbonate on your blood phosphorus levels, FGF23 levels, and associated phosphorus regulatory hormone levels, and (2) to monitor for safety and side-effects. However, we would like to store some of your blood and urine samples and health information for future research related to the area of chronic kidney disease, cardiovascular disease, and bone disease. We will label all your samples with a unique study code instead of your personal health identifiers to protect your privacy.

Some of your blood and urine specimens will be sent to the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) Repository, a research resource supported by the National Institutes of Health. The purpose of this collection is to make samples available for use in research for the study of chronic kidney disease, cardiovascular disease, and bone disease after the current study is completed. Sending samples to the Repository may give scientists valuable research material that can help them to develop new diagnostic tests, new treatments, and new ways to prevent diseases. These specimens will also be labeled by a unique code and without your personal health identifiers. Therefore, the Repository will not be able to give out your name, or other information that identifies you to the scientists who receive the samples.

This study will not collect or use any genetic data, now or at any time in the future. Your sample will be used only for research and will not be sold. The research done with your tissue and blood sample may lead to the development of new products in the future. No compensation will be given to you now or in the future for the use of these samples.

Requests for samples: An appropriate external panel will review all requests to use Repository samples. That panel will include a bioethicist and other individuals with expertise in one or more areas including; clinical research, epidemiology, physiology, statistical analysis, and molecular genetics research. NIH Program and Review staff are excluded from membership on this panel, but can provide appropriate guidance, background information, and technical assistance.

Specimens will not be used for genetic research.

Please initial one option below to indicate your preference:

_____ I consent to banking of my blood and urine specimens for future research.

_____ I do not consent to banking of my blood and urine specimens for future research.

Re-contact: Dr. Wolf and his associates may conduct future studies in patients with kidney disease, and may wish to contact you about your interest in participating in future trials. Please initial one option below to indicate your preference:

_____ I consent to re-contact for participation in future studies.

_____ I do not consent to re-contact for participation in future studies.

The following section calls for you to indicate your choice for optional procedures that you do not have to agree to in order to participate in the main study.

Cardiac MRI Scans:
Please initial your choice:

_____ I consent to having a Cardiac MRI.

_____ I do not consent to having a Cardiac MRI.

Renal MRI Scans:
Please initial your choice:

_____ I consent to having a Renal MRI.

_____ I do not consent to having a Renal MRI.

Consent Summary:
I have read this consent form and the research study has been explained to me. I have been given time to ask questions, and have been told whom to contact if I have more questions. I agree to be in the research study described above. A copy of the consent form will be provided to me after I sign it.

A copy of this signed consent document, information about this study and the results of any test or procedure done may be included in my medical record and may be seen by my insurance company.

_____ _____
Subject's Name (printed) and Signature Date

_____ _____
Name (printed) and Signature of Person Obtaining Consent Date