SHORT-TERM EFFECTS OF NICOTINAMIDE AND LANTHANUM CARBONATE ON PHOSPHORUS HOMEOSTASIS IN HEALTHY VOLUNTEERS

Detailed physiologic study of healthy volunteers

Principal Investigator:

Tamara Isakova, MD, MMSc
Northwestern University
Address: 633 North St. Clair, 18th Floor
Room 18-083
Chicago, IL 60611
Phone # (312)-503-6921
Fax # (312)-503-5656
Email: tamara.isakova@northwestern.edu

Biostatistician: Jungwha Lee, PhD
Assistant Professor, Department of Preventative Medicine
Northwestern University
680 N Lake Shore Drive
Suite 1400
Chicago, IL 60611
(312)-503-2292
Fax: (312)-908-9588
jungwha-lee@northwestern.edu

Study Drug/Study Device: Nicotinamide
Lanthanum carbonate, Fosrenol

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Research Office Address
633 North St. Clair, 18th Floor
Room 18-083
Chicago, IL 60611
Phone # (312)-503-6921
Fax # (312)503-5656
Email: tamara.isakova@northwestern.edu

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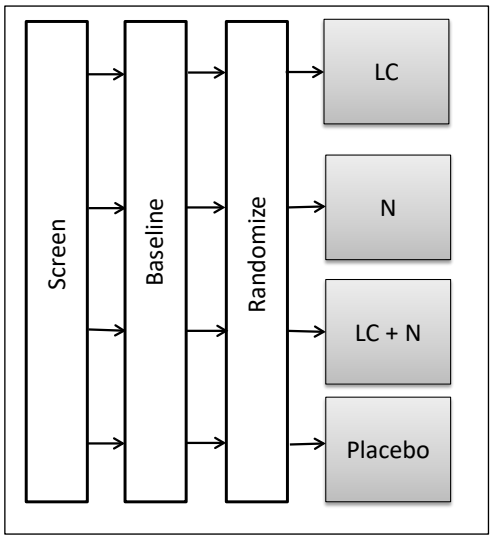
LIST OF ABBREVIATIONS

CKD	chronic kidney disease
CBC	complete blood counts
CVD	cardiovascular disease
ESRD	end-stage renal disease
FGF23	fibroblast growth factor 23 hormone
LVH	left ventricular hypertrophy
NPT2b	sodium phosphate co-transporter
PTH	parathyroid hormone
FEPi	Fractional excretion of phosphate
P1NP	N terminal propeptide of Type 1 procollagen, bone formation marker
CTX	C terminal cross-linked peptide, bone resorption marker
LC	Lanthanum Carbonate
N	Nicotinamide

STUDY SCHEMA



LC, Lanthanum carbonate
N, Nicotinamide

STUDY SUMMARY

Title	**EFFECTS OF NICOTINAMIDE AND LANTHANUM CARBONATE ON PHOSPORUS HOMEOSTASIS**
Short Title	**Nicotinamide, lanthanum carbonate and phosphate homeostasis**
Protocol Number	The standard protocol number used to identify this study
Phase	Phase 1, detailed physiologic study
Methodology	double blind, randomized, placebo-controlled, 2x2 factorial
Study Duration	12-18 months (to complete the entire study protocol)
Study Center(s)	Single-center
Objectives	Define short-term effects of the interventions (lanthanum carbonate and nicotinamide) on indices of phosphate handling
Number of Subjects	80
Diagnosis and Main Inclusion Criteria	Healthy volunteers
Study Product(s), Dose, Route, Regimen	Nicotinamide, 750 mg by mouth twice daily Lanthanum carbonate, Fosrenol, 1000 mg by mouth three times daily with meals
Duration of administration	2 weeks (length of time study participants are enrolled in study)
Reference therapy	reference is a placebo
Statistical Methodology	Repeated measures analysis using mixed linear models

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Chronic kidney disease (CKD) is a growing public health problem that increases risks of end-stage renal disease (ESRD), cardiovascular disease (CVD), fractures, and death, and it poses an enormous financial burden on the US health system.[1-3] Existing therapies modestly impact outcomes.[4-8] Novel strategies targeting CKD-specific mechanisms are urgently needed to improve health and reduce cost.

CKD is complicated by disordered mineral metabolism, characterized by abnormal calcium and phosphate homeostasis, calcitriol and klotho deficiency, and elevated levels of parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23).[9] Elevated FGF23 is the earliest and most common manifestation of disordered mineral metabolism.[10] Observational studies report independent associations between elevated phosphate and FGF23 blood levels and increased risks of ESRD, CVD and death.[11-13] As potential explanatory mechanisms, phosphate excess induces arterial stiffness due to vascular calcification, and FGF23 excess contributes directly to the pathogenesis of left ventricular hypertrophy (LVH).[14,15] Together, these effects promote CVD events and death.[12]

Dietary phosphate absorption is a modifiable determinant of phosphate and FGF23 levels.[16-18] Small studies of short duration suggest that phosphate binders and dietary phosphate modification in CKD can lower phosphate and FGF23 blood levels by reducing paracellular absorption of phosphate in the gut.[19] However, animal studies demonstrate that compensatory upregulation of transcellular phosphate absorption via the sodium phosphate co-transporter, NPT2b, reduces the efficacy of these approaches.[20,21] Since nicotinamide lowers plasma phosphate by reducing gut expression of NPT2b,[22] we hypothesize that use of nicotinamide combined with phosphate binders on a background of dietary phosphate moderation will most effectively reduce phosphate and FGF23 blood levels in CKD. We plan to advance this approach in future randomized clinical trials.

The objective of this study is to perform a detailed physiologic study of healthy volunteers to assess the short-term effects of nicotinamide alone, lanthanum carbonate alone, or both in combination, on phosphate homeostasis. The results from healthy volunteers will provide information needed for optimal design of studies for patients with CKD.

1.2 Study Agent(s)/Devices Background and Associated Known Toxicities

Nicotinamide will be used at a dose of 750 mg twice daily. Nicotinamide reduces plasma phosphate levels by blocking intestinal phosphate absorption through down-regulation of NPT2b,[21] and it is well-tolerated and considered safe at high doses.[23] Unlike niacin, nicotinamide does not cause flushing, and is thought to be less likely to cause liver test abnormalities, hyperuricemia, or insulin resistance.[24] In a post-hoc analysis of a randomized study of niacin in 327 patients with CKD stages 2 and 3, Rao et al found that, in addition to reducing phosphate levels in the blood, niacin decreased FGF23 levels by 10.9% from baseline over 24 weeks, and that the magnitude of the decline in FGF23 was directly associated with the magnitude of decline in blood phosphate.[25]

Lanthanum carbonate at a dose of 1000 mg twice daily with meals will be used. Lanthanum carbonate is a phosphate binder that is approved for use in patients with ESRD undergoing dialysis. This fixed dose was chosen because we have demonstrated that this dose safely reduced urinary phosphate, signifying effective phosphate binding, in CKD stages 3–4.[26,27] Importantly, lanthanum carbonate has been used in the hemodialysis population, with 6-year long safety data demonstrating a good safety profile.[28] Lanthanum carbonate has also been

used in healthy volunteers in whom it has also been found to be safe. As in patients with CKD, doses of 1000 mg three times daily in healthy volunteers achieve maximal reduction in 24-hour urine.[29]

1.3 Other Agents/Devices

N/A

1.4 Rationale

The justification for the combined approach of binders with nicotinamide to modify plasma phosphate and FGF23 levels in CKD is rooted in our current understanding of the underlying biology. However, detailed human physiologic studies investigating the joint effects of these agents on blood and urine levels of mineral metabolites are not available in health or in CKD. Animal data consistently demonstrate that nicotinamide blocks small bowel Pi absorption by decreasing protein levels of NaPi2b.[20,21] Some studies also suggest that nicotinamide may block phosphate reabsorption at the renal proximal tubule,[30] but this has not been studied in detail in healthy volunteers or CKD patients. Finally, the effects of nicotinamide on FGF23, PTH, calcitriol, and other parameters of mineral metabolism are unexplored in humans. Therefore, our proposed study will fill critical gaps that are needed to advance this novel therapeutic approach into future clinical trials.

We propose to study healthy volunteers because detailed data on the effects on mineral metabolism of nicotinamide alone or in combination with binders in this population are not available. In the future, we will also extend the proposed studies to patients with CKD.

Given that 24-hr urinary phosphate excretion declines and fractional phosphate excretion rises with progressive CKD, an additional justification for the study of healthy volunteers is the ability to easily detect changes following proposed interventions in both 24-hour and fractional urinary phosphate excretion.

For this detailed physiologic study, we chose to use the 2x2 factorial study design because we are specifically interested in investigating the effects of the combined interventions as compared to the effects of the placebo and to each monotherapy group.

We chose plasma phosphate, 24-hour urine phosphate, fractional urinary excretion of phosphate (FEPI), FGF23 and PTH as end-points because we are interested in the effects of the interventions on phosphate handling and mineral metabolism (See Table). Additional end-points will include markers of bone turnover, including N terminal propeptide of Type 1 procollagen (P1NP) and C terminal cross-linked peptide (CTX) to assess the influence of the interventions on bone metabolism.

Summary of End Points

End-Point	Primary	Secondary	Justification
Plasma Phosphate	X		Marker of phosphate handling
24-hr Urine Phosphate	X		Marker of phosphate handling
FePI	X		Marker of phosphate handling
PTH		X	Hormonal regulator of mineral metabolism
FGF23		X	Hormonal regulator of mineral metabolism
P1NP		X	Bone formation marker
CTX		X	Bone resorption marker

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the short-term effects of lanthanum carbonate and nicotinamide, alone and in combination, on phosphate handling, as measured by plasma phosphate, 24-hour urinary phosphate and fractional excretion of phosphate in healthy volunteers

2.2 Secondary Objectives

2.2.1 To determine the short-term effects of lanthanum carbonate and nicotinamide, alone and in combination, on hormonal regulators of mineral metabolism: FGF23 and PTH

2.2.2 To determine the short-term effects of lanthanum carbonate and nicotinamide, alone and in combination, on markers of bone turnover: P1NP and CTX

2.3 Endpoints

Summary of End Points			
End-Point	**Primary**	**Secondary**	**Justification**
Plasma Phosphate	X		Marker of phosphate handling
24-hr Urine Phosphate	X		Marker of phosphate handling
FePI	X		Marker of phosphate handling
PTH		X	Hormonal regulator of mineral metabolism
FGF23		X	Hormonal regulator of mineral metabolism
P1NP		X	Bone formation marker
CTX		X	Bone resorption marker

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Healthy volunteers

3.1.2 Age ≥ 18 years, at the time of screening

3.1.3 Normal renal function at screening, as defined by
- eGFR > 60
- no albuminuria
- normal urinalysis
- normotensive, defined as blood pressure <140/85mmHg
- no known history of CKD

3.1.4 Adequate organ and marrow function at screening as defined below:
- HCT ≥ 30%
- platelets ≥ 125,000/mm^3

- total bilirubin within normal institutional limits

- AST(SGOT)/ALT(SPGT) ≤ 2.5 X institutional upper limit
- 25-hydroxyvitamin D ≥ 10mg/dL

3.1.5 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for *90* days following completion of therapy.

3.1.6 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 History of allergic reaction to nicotinamide, niacin (excluding flushing), and/or multivitamin preparations
3.2.2 Liver disease, defined as known cirrhosis by imaging or physician diagnosis, documented alcohol use > 14 drinks/week, or aspartate aminotransferase (AST), alanine aminotransferase (ALT), and/or alkaline phosphatase concentrations > 2 times the upper limit of the local laboratory reference range and/or total bilirubin concentration not within institutional limits.
3.2.3 Creatine kinase (CK) concentrations > 2 times the upper limit of the local laboratory reference range at screening
3.2.4 Major hemorrhagic event within the past six months from screening requiring in-patient admission
3.2.5 Blood or platelet transfusion within the past six months from screening
3.2.6 History of primary hyperparathyroidism
3.2.7 Current, clinically significant malabsorption
3.2.8 Anemia (screening HCT < 30%) at screening
3.2.9 Plasma albumin < 2.5 mg/dl at screening
3.2.10 25-hydroxyvitamin D <10mg/dL at screening
3.2.11 Inability or unwillingness to travel to study visits, as described in the protocol
3.2.12 Inability or unwillingness to provide consent
3.2.13 Current or recent treatment (within the last 14 days from screening) with niacin/nicotinamide > 100 mg/day
3.2.14 Current or recent use of MVI containing niacin/nicotinamide > 100 mg/day
3.2.15 Current use of Tums (or calcium carbonate taken for indigestion) at a dose of >1000 mg daily
3.2.16 Current participation in another clinical trial or other interventional research

3.3 WOMEN OF CHILD-BEARING POTENTIAL

3.3.1 Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

- Pregnancy or planning to become pregnant or currently breast-feeding. Women of childbearing potential (pre-menopausal and not surgically sterilized) will have pregnancy test before enrollment

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

4.1.1 Overview:
Eligible participants will be randomized to one of the following 4 groups:
- Lanthanum carbonate + nicotinamide
- Lanthanum carbonate + nicotinamide placebo
- Lanthanum carbonate placebo + nicotinamide
- Lanthanum carbonate placebo + nicotinamide placebo

4.1.2 Regimen description is presented in the table below.

Agent	Dose	Route	Schedule	Cycle Length
Nicotinamide	750 mg twice daily	By mouth	Daily for 2 weeks	2 weeks (14 days)
Lanthanum carbonate	1000 mg three times daily with meals	By mouth	Daily for 2 weeks	

Lanthanum carbonate is a chewable tablet. Lanthanum carbonate binds ingested phosphorus in the gut and therefore only works when taken with meals. Participants who do not eat regular meals will be instructed to take full doses with larger meals and half with snacks. Nicotinamide can be taken together with lanthanum carbonate at breakfast and at dinner.

4.2 Toxicities and Dosing Delays/Dose Modifications

Lanthanum carbonate may lower blood phosphate levels and can be associated with gastrointestinal side effects including nausea, vomiting, constipation and diarrhea.

Nicotinamide may lower blood phosphate levels and may be associated with other laboratory abnormalities including thrombocytopenia, abnormalities in liver function tests and CK. Gastrointestinal side effects, such as diarrhea and heartburn may also occur.

The following laboratory results are **expected study adverse events**:
- **Hypophosphatemia**: Plasma phosphate level <1.5 mg/dl
- **Thrombocytopenia**: Platelet count <100,000
- **Liver function test abnormalities**: AST, ALT, total bilirubin, alkaline phosphatase> 4 times the upper limit of the core lab (fill in precise numbers when the lab is named)
- **Elevated Creatine Kinase:** Creatine Kinase > 4 times upper limit of normal

The following symptoms are **expected study adverse events**:

- **Bruising**
- **Bleeding**
- **Severe diarrhea**
- **Severe nausea**
- **Flushing**
- **Hives**

Each patient will be assessed for the development of toxicity at each study visit (see section 5.4).

4.3 Concomitant Medications/Treatments

Calcium carbonate tablets taken for indigestion, such as Tums, are allowed if taken once per day or less, at least 2 hours away from meals and at a maximum dose of 1000 mg daily. However, participants who report using Tums often will be encouraged to try over-the counter Pepcid (famotidine), Tagamet (cimetidine), or Zantac (ranitidine).

Non-study source of vitamin B3 (niacin or nicotinamide) as a stand- alone medication or in a multivitamin that contains less than 100 mg/day of nicotinamide is allowed. Larger doses are to be avoided.

4.4 Other Modalities or Procedures

N/A

4.5 Duration of Therapy

The intervention will last for 2 weeks.

4.6 Duration of Follow Up

Follow up will last for 2 weeks.

4.7 Removal of Participants from Protocol Therapy

Patients will be removed from therapy when any of the criteria listed in Section 5.6 apply.

4.8 Participant Replacement

N/A

5.0 STUDY PROCEDURES

There are 8 expected visits for the entire study. Study visits baseline 1 and follow-up 5 will take place at the NUCATS Clinical Research Center (CRU). The remaining visits will be completed at the Center for Translation Metabolism and Health (CTMH).

5.1 *Recruitment*

Subjects will be recruited using the NUCATS registry, Women's Health Research Institute registry, Illinois Men's Health Registry, ResearchMatch registry, newspaper and online advertisements, and an IRB-approved flyer. Potential participants from the registries will be sent an IRB-approved recruitment letter, recruitment e-mail, and contacted via telephone. Individuals solicited via Women's Health Registry and Men's

Health Registry will be sent recruitment letters specific to the registry. Newspaper and online advertisements will use IRB-approved advertisement.

5.2 Screening Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent.

The screening procedures include:

5.2.1 *Informed Consent*

Consent form will be reviewed in full with each subject.

5.2.2 *Medical history and Physical Exam*

Complete medical and surgical history will be obtained from each subject, and a physical exam will be performed on each subject.

5.2.3 *Demographics*

Subject will be queried on age, gender, race, and ethnicity

5.2.4 *Review subject eligibility criteria*

Study personnel will review inclusion/exclusion criteria with every subject to determine eligibility.

5.2.5 *Review previous and concomitant medications, including multivitamins*

5.2.6 *Vital signs, height and weight*

Blood pressure, height, and weight will be obtained on each subject.

5.2.7 *Hematology*

CBC

5.2.8 *Plasma chemistries and Serum 25-Hydroxyvitamin D*

To include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, chloride, bicarbonate), glucose, and total bilirubin; phosphorus; calcium; CK; and 25-hydroxyvitamin D

5.2.9 *Random urine*

To include: creatinine and albumin

5.2.10 *Supplies for 24-hr urine collection*

5.2.11 *Rapid Urine Pregnancy test (for females of child bearing potential)*

See section 3.1.6.1 for definition.

5.3 Baseline Procedures

During this period, we will get baseline assessments of parameters of interest.

5.3.1 Baseline Visit 1

- Return 24-hour urine collection to measure phosphorus, creatinine, calcium, and urea in the urine
- Random urine sample to measure phosphorus, creatinine, and calcium in the urine
- 8-hour CRU stay for 8–hour timed urine collection to measure phosphorus, creatinine, calcium and urea in the urine
- Plasma chemistries (creatinine, phosphate, calcium)
- Blood draw for correlative studies (PTH, FGF23, P1NP, CTX)
- Blood draw for optional study elements (PTH, FGF23, P1NP, CTX)
- Distribute supplies for 24-hr urine collection

5.4 Procedures During Treatment

During this period, participants will be randomized to the intervention arms (Baseline 2/ Follow up visit 0), have two 8-hour visits (Baseline visits 1 and Follow up visit 5) and will make visits to the CTMH every 3 days (Follow up visits 1 – 4).

5.4.1 Baseline 2/Follow-up Visit 0 (F0)

- Return 24-hour urine collection to measure phosphorus, creatinine, calcium, and urea in the urine
- Random urine sample to measure phosphorus, creatinine, and calcium in the urine
- Plasma chemistries (NA, K, Cl, HCO3, BUN, Cr, glucose, phosphate, calcium)
- Blood draw for correlative studies (PTH, FGF23)
- Randomization to interventions
- Distribute study drug/placebo
- Distribute supplies for next 24-hr urine collection

5.4.2 Follow-up Visits 1 – 4 (F1-F4)

- Return 24-hour urine collection to measure phosphorus, creatinine, calcium, and urea in the urine
- Plasma chemistries(NA, K, Cl, HCO3, BUN, Cr, glucose, calcium)
- Blood draw for correlative studies (PTH, FGF23)
- Random urine sample to measure phosphorus, creatinine, and calcium in the urine
- Distribute supplies for next 24-hr urine collection
- Bring in pill bottles for pill counts
- Safety assessments (phosphate, CK, CBC, LFTs, GI Questionnaire)

5.4.3 Follow-up Visit 5 (F5)

- Return 24-hour urine collection to measure phosphorus, creatinine, calcium, and urea in the urine
- Random urine sample to measure phosphorus, creatinine, and calcium in the urine
- 8-hour CRU stay for 8–hour timed urine collection to measure phosphorus, creatinine, calcium and urea in the urine

- Plasma chemistries (NA, K, Cl, HCO3, BUN, Cr, glucose, calcium)
- Safety assessments (phosphate, CK, CBC, LFTs, GI Questionnaire)
- Blood draw for correlative studies (PTH, FGF23, P1NP, CTX)
- Blood draw for optional study elements (PTH, FGF23, P1NP, CTX)
- Bring in pill bottles for pill counts

5.5 Time and Events Table

Periods	**SCREENING**	**BASELINE**		**Follow UP**				
Visits	**S1**	**B1**	**B2/F0**	**F1**	**F2**	**F3**	**F4**	**F5**
Days	**-15**	**-5**	**-2**	**0**	**3**	**6**	**9**	**12**
Pregnancy testing	X							
RANDOMIZATION			X					
Distribute drug/placebo (X=21 day supply)			X					
Demographics, medical history, physical exam	X							
Vital signs (blood pressure, height, weight)	X							
Co-Primary end-points								
FePI/ Spot Urine phosphate, calcium, and creatinine		X	X	X	X	X	X	X
24-hr urine phosphate, creatinine, calcium, and urea		X	X	X	X	X	X	X
8 hr urine phosphate, creatinine, calcium, and urea		X						X
Spot Urine (creatinine, albumin)	X							
Other mineral metabolites								
PTH		X	X	X	X	X	X	X
FGF23		X	X	X	X	X	X	X
P1NP (bone metabolism marker)		X						X
CTX (bone metabolism marker)		X						X
25 hydroxyvitamin D	X							
Plasma Phosphate	X	X	X	X	X	X	X	X
Plasma Calcium	X	X	X	X	X	X	X	X
Renal parameters								
Chem 7 (Na, K, Cl, HCo3, BUN, Cr, glucose)	X		X	X	X	X	X	X
Plasma Creatinine		X						
Stored blood samples (optional)		X						X
Stored urine samples (optional)		X						X
CBC, LFTs, CK	X			X	X	X	X	X
Adverse events assessment (labs and GI questionnaire)				X	X	X	X	X
Pill Count				X	X	X	X	X

5.6 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented.

6.0 Response Criteria

Plasma Phosphate levels, CBC, LFTs, CK will be monitored as safety labs through the intervention period.

6.1 Safety/tolerability

Analyses of safety will be performed for all patients having received at least one dose of study drug.

7.0 ADVERSE EVENTS

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug/device, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Definitions

7.2.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

7.2.2 Severity of Adverse Events

The severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

7.2.3.1 Results in death.
If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

7.2.3.2 Is life-threatening.
(the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

7.2.3.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

7.2.3.4 Results in persistent or significant disability or incapacity.

7.2.3.5 Is a congenital anomaly/birth defect

7.2.3.6 Is an important medical event
Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“. For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event

Step 2: Grade the adverse event

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

7.4 Reporting Requirements for Adverse Events

7.4.1 Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- The IRB must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

7.4.2 Routine Reporting

- All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

7.5 Unblinding Procedures

When a participant stops his or her blinded nicotinamide and lanthanum carbonate and appropriate clinical management of the participant is dependent on knowledge of whether the participant had been taking active nicotinamide or active lanthanum carbonate, the research pharmacist will unblind the investigator to the necessary arm.

7.6 Stopping Rules

7.6.1 Hypophosphatemia

If a study participant has a plasma phosphate level lower than 1.5 mg/dl, an extra visit will be held immediately so the test can be repeated. If the second lab test confirms a plasma phosphate level under 1.5 mg/dl, then both study medications should be stopped.

7.6.1 Other side effects

If a study participant develops any of the following expected study adverse events, study interventions will be stopped:

- Thrombocytopenia: Platelet count <100,000
- Liver function test abnormalities: AST, ALT, total bilirubin, alkaline phosphatase> 4 times the upper limit of the core lab (fill in precise numbers when the lab is named)
- Elevated Creatine Kinase: Creatine Kinase > 4 times upper limit of normal
- Severe bleeding
- Severe diarrhea
- Severe nausea
- Severe Flushing
- Hives

8.0 DRUG/DEVICE INFORMATION

8.1 Lanthanum Carbonate

- Fosrenol
- Classification – phosphate binder
- Mode of action: binds intestinal phosphate
- Storage and stability: stable at room temperature; protect from moisture
- Protocol dose: 1000 mg by mouth three times daily with meals
- Preparation: chewable tablet
- Route of administration for this study: by mouth

- Incompatibilities: N/A
- Availability: provided free of charge by manufacturer
- Side effects: hypophosphatemia, nausea, vomiting, diarrhea, abdominal discomfort
- Nursing implications: none

8.2 Nicotinamide

- Niacinamide
- Classification – vitamin
- Mode of action: blocks phosphate absorption through gut sodium phosphate channel
- Storage and stability: stable at room temperature; protect from moisture
- Protocol dose: 750 mg by mouth twice daily
- Preparation: tablet, oral
- Route of administration for this study: by mouth
- Incompatibilities: N/A
- Availability: provided free of charge by manufacturer
- Side effects: hypophosphatemia, nausea, vomiting, diarrhea, abdominal discomfort
- Nursing implications: none

8.2.1 Return and Retention of Study Drug/Device

The research pharmacist at NMH will assist with disposal of drugs.

8.1.2 We will use pill counts to document compliance with drugs.

9.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to understand how changes in phosphate homeostasis affect endocrine regulators of bone and mineral metabolism and markers of bone turnover. Additional stored samples will be archived for future analyses of newly discovered biomarkers related to bone and mineral homeostasis and its regulation. Submission of samples for correlative studies is mandatory. The consent form will have a statement that will inform participants about the planned use of archived samples. Participants who chose not to have their samples archived may opt out.

9.1 Sample Collection Guidelines

We will collect blood (serum and plasma) and urine samples. Samples will be labeled with the subject's de-identified study number and collection date and delivered for storage to the team's freezers. Samples will be processed at the NUCATS CRU laboratory.
Samples will be collected at the intervals indicated in section 5.5.

9.2 Assay Methodology

Specialized assays include**: FGF23** ELISA (Immutopics, CA); **N terminal propeptide of Type 1 procollagen** (P1NP) ELISA (USCN Life Science, Houston, TX); and **C terminal cross-linked peptide** (CTX) ELISA (Immunodiagnostic Systems, Scottsdale, AZ). All measurements of specialized assays will be performed at specialized labs at Feinberg School of Medicine once the study has ended.

Standard assays (plasma and urinary calcium, phosphate and creatinine, LFTs, CBC, PTH) will be performed at NMH clinical labs.

9.3 Specimen Banking

Patient samples collected for this study will be retained in the study freezers located at CTMH at 633 N. St. Clair, Suite 18-098,Chicago, IL, 60611 and/or in the Freezer Farm at the Tarry Research Building at 300 East Superior Street Chicago, IL 60611. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Dr. Tamara Isakova will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of NU. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of NU for publication and any licensing agreement will be strictly adhered to.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by NU, the investigator or a collaborating researcher or entity.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Collection time in relation to study treatment
- Demographic data
- De-identified stored samples

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a 2-week, randomized, double-blinded, 2x2 factorial design study of 80 healthy volunteers (20 in each of the four treatment groups) investigating the effects of the

interventions on changes in plasma and urinary phosphate. Participants will be randomized to one of the four groups: 1) lanthanum carbonate + nicotinamide; 2) lanthanum carbonate + nicotinamide placebo; 3) lanthanum carbonate placebo + nicotinamide; 4) lanthanum carbonate placebo + nicotinamide placebo.

The end-points are listed in the table below:

Summary of End Points			
End-Point	**Primary**	**Secondary**	**Justification**
Plasma Phosphate	X		Marker of phosphate handling
24-hr Urine Phosphate	X		Marker of phosphate handling
FePI	X		Marker of phosphate handling
PTH		X	Hormonal regulator of mineral metabolism
FGF23		X	Hormonal regulator of mineral metabolism
P1NP		X	Bone formation marker
CTX		X	Bone resorption marker

10.2 Sample Size and Accrual

Assumptions based on prior studies:

- Data on effects of nicotinamide on blood or urine phosphate in healthy volunteers are not available.
- Similiarly, data on the combined use of the nicotinamide and lanthum carbonate are lacking.
- Therefore, we relied on published data of the effects on lanthanum carbonate on 24-hour urine phosphate. In previous short-term studies of healthy volunteers, lanthanum carbonate at the dose that we will use in our study decreased 24-hour urine phosphate by 236 to 468 mg/day.[29] The within group standard deviation of change in 24-hour urine phosphate ranged from 168 to 294 mg/day.[29]

Derivation of the sample size for this study:

Using the PS Power and Sample Size calculator (independent t test), we estimated that a sample size of 20 participants per group will yield 80% power to detect a difference of 273 mg/dl in urine phosphate, at α=0.05, assuming a within group SD of the change in 24-hour urine phosphate of 300 mg/day. Assuming a conservative within group SD of the change in plasma phosphate of 0.55 mg/dl, the sample size of 20 volunteers per group will allow us to detect a difference as small as 0.50 mg/dl in plasma phosphate.

Importantly, we based our power calculations on t-tests that compare pre to post intervention changes across two groups. Because the repeated measures analyses we will employ using linear mixed models will reduce within-subject variability, we expect to have more power than is tabulated above and view the presented power calculations as conservative estimates. Additionally, power for main effects analyses (effects of lanthanum carbonate alone and nicotinamide alone; 40 participants per groups; margin comparison) will be greater than the presented power for comparisons of dual treatment to placebo (20 participants per group; individual cell comparison).

10.3 Data Analyses Plans

- We will study changes over time in absolute levels of the primary and secondary end-points.
- We will use mixed-model, repeated-measures analyses to assess the changes.
- Model terms will include:
    - fixed-effects treatment terms (treatment group);
    - the interaction between each treatment and time (nicotinamide x time and lanthanum carbonate x time);
    - the interaction between treatments (nicotinamide x lanthanum carbonate);
    - the interaction between treatments and time (nicotinamide x lanthanum carbonate x time);
    - random-effects terms, connoting individual participants.
- If the interaction term between treatments and time (nicotinamide x lanthanum carbonate x time) is significant, we will compare the response in the dual intervention group to the placebo group.
- If the interaction term between treatments and time (nicotinamide x lanthanum carbonate x time) is not significant, we will examine the main effects of each intervention.
- We will use natural log transformation for end points with skewed distribution.
- If there are significant differences ($p<0.05$) in age, gender and baseline eGFR across randomized treatment groups, we will adjust for these covariates.
- Standard descriptive analyses will be used for safety evaluations.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Feinberg School of Medicine. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.3 Registration Procedures

N/A

11.4 Subject Compensation

Subjects will receive compensation per study consent form. Study compensates $50.00, in the form of a check, for each of the 8 study visits. Total compensation, excluding reimbursement for travel expenses, is $400.00. Subjects will be required to submit proof of travel expenses (i.e., receipts) to study staff in order to be reimbursed for travel expenses. Travel expenses will be paid out in the form of a check as well.

11.5 Data Management and Monitoring/Auditing

The PI and Co-I will monitor data safety monitoring/management.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within five (5) business days of making the change.

11.6.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.

- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

11.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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13.0 APPENDICES

Appendix A.
Letter of IND exemption from the FDA