TITLE

A Sequential Dose Escalation Study to Assess Human Pharmacokinetics of Orally Administered Strontium *L*-lactate

Protocol BIO-1703

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CONFIDENTIAL

CLINICAL INVESTIGATOR PROTOCOL SIGNATURE SHEET

Protocol BIO-1703

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By my signature below, I attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this protocol (including appendices). I will not initiate this study without approval from the appropriate Institutional Review Board (IRB) and I understand that any changes to the protocol must be approved in writing by the Sponsor and the IRB before they can be implemented, except where necessary to eliminate immediate hazards to the subject.

Approval Signatures:

Andrea Lawless, MD — Mar 09, 2017

Clinical Investigator Signature **Date**

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SPONSOR PROTOCOL SIGNATURE SHEET

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By my signature below, I approve of this protocol.

Sponsor Company: Deanna J. Nelson 3 March 2017
Signature Date

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1. List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
C_{max}	maximal concentration
CO_2	carbon dioxide
d	day
dL	deciliter
eCRF	electronic case report form
EE	efficacy evaluable
fax	facsimile
FDA	Food and Drug Administration
GI	gastrointestinal
g	gram
GCP	good clinical practice
$t_{1/2}$	half life
h	hour
HIPAA	Health Insurance Portability and Accountability Act
iAUC	incremental area under the curve
ICH	International Conference on Harmonization
IRB	Institutional Review Board
kg	kilogram
MCH	mean corpuscular height
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
m^2	meter squared
mg	milligram
min	minute
mL	milliliter
mm Hg	millimeters of mercury
oz	ounce
PP	per protocol
PK	pharmacokinetic
λ_z	rate of elimination
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	standard operating procedure
Sr	strontium
T_{max}	time to maximum concentration
WBC	white blood cell

2. Background/Rationale

Osteoporosis is a global health concern. According to the National Institutes of Health, approximately 10 million Americans have osteoporosis. Typically, an individual is not aware of the disease until an unexpected fracture of the leg, hip, or spine occurs. It is estimated that at least one-half of adult women and 1 in 5 adult men over the age of 50 will sustain one or more vertebral, hip or other fractures in their lifetime. The annual acute costs and subsequent costs of care related to treating osteoporotic-related injuries are estimated to be over $14 billion. Osteopenia, a condition of around 34 million more Americans, is marked by a loss in bone mass. Frequently, osteopenia serves as "an early warning" that bone loss has started but progression can be slowed or halted by changes in life style and/or use of preventive measures or medications (Office of the Surgeon General 2004; Wright 2014).

In general, bone health can easily be maintained throughout life. Getting sufficient calcium from the diet throughout life helps to build and maintain strong bones. Since vitamin D upregulates calcium receptors and aids in calcium utilization by the body, eating foods that are rich in this vitamin and getting sufficient exposure to sunlight to aid the conversion to the active form, complement intake of dietary calcium. Finally, including regular weight-bearing exercise adds "muscle" to one's bone-health regimen.

If these actions are not sufficient to maintain bone health, several medicines are known to slow bone loss and treat osteoporosis when administered together with calcium and vitamin D. Strontium salt is one such medication. The strontium salt that is currently most widely used to treat osteoporosis is PROTOS® (strontium ranelate). Clinical studies in adults with osteoporosis have demonstrated that PROTOS reduces the incidence of fractures (both vertebral and non-vertebral) and increases bone mass and bone mineral density (Reginster 2012; Deeks 2010; Slosman 1994). Strontium salts have been safely administered to both normal subjects and subjects with osteoporosis at a daily dose as high as 2 g and for dosing periods as long as three years.

Stratum Plus™, is a highly pure form of strontium *L*-lactate (the strontium salt of *L*-lactic acid). Stratum Plus is manufactured in compliance with current Good Manufacturing Practices. The product has been thoroughly tested and meets rigorous purity specifications. It is free from contamination by *D*-lactic acid and trace metals known to harm human health. Unlike strontium renalate (and other related strontium salts), no clinical trials have been conducted with Stratum Plus. Thus, this study will be conducted to obtain pharmacokinetic (PK) information following acute oral intakes of three doses of Stratum Plus in healthy adults.

3. Objectives

The objective of this clinical trial is to obtain PK information following acute oral intakes of three doses of Stratum Plus in healthy adults.

4. Study Sample Population

Subjects will be healthy men and women 18-65 years of age, inclusive, with a body mass index (BMI) 18.0 to 31.9 kg/m^2. Subjects must also exhibit a body weight >60 kg, inclusionary.

5. Study Design and Procedures

5.1 Study Product

- Low dose (170 mg Sr) strontium *L*-lactate
- Medium dose (340 mg Sr) strontium *L* -lactate
- High dose (680 mg Sr) strontium *L* -lactate

The study product will be provided as a dry powder and will be diluted in distilled water for consumption.

5.2 Study Design

This is an unblinded, crossover, sequential three dose study (Figure 1). The study will include one screening visit (Visit 1; day -7) and three test visits (Visits 2, 3, and 4; days 0, 7, and 14) with at least a 6-d washout between test visits.

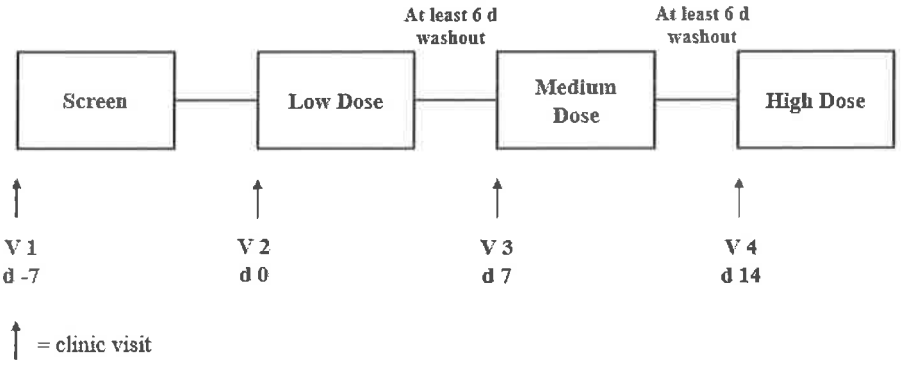

Figure 1.

At Visit 1 (day -7), subjects will provide informed consent and undergo screening assessments including evaluations of medical history, prior/current medication/ supplement use, inclusion and exclusion criteria, height, body weight, BMI, vital signs, and Vein Access Scale (Appendix 2). A fasting capillary blood glucose will be assessed to establish each subject's fasting level and an in-clinic urine pregnancy test (all women <60 years of age) will also be obtained. Additionally, a fasting (10-14 h) blood sample will be collected for a chemistry profile and hematology panel. Study instructions will also be provided [fasting compliance (10-14 h, water only) and avoidance of alcohol 3 d

prior to test visits (Visits 2, 3, and 4; days 0, 7, and 14]. Subjects will then be dispensed a 24-h Diet Record (Appendix 3) with instructions to record intake the day prior to Visit 2 (day 0).

At Visit 2 (day 0), subjects will arrive at the clinic fasted (10-14 h, water only, anchored to the t = -0.25 h blood draw) for the 12-h PK test visit. Subjects will undergo clinic visit procedures including: a review of inclusion/exclusion criteria, concomitant medication/supplement use, body weight, and vital signs assessment. Adverse events (AE) will be assessed and subjects will be queried about study instructions compliance. Additionally, the 24-h Diet Record will be collected and reviewed. A fasting capillary blood glucose will be assessed to confirm fasting status. Eligible subjects will be enrolled and will begin the PK test with the insertion of an intravenous catheter at least 5 min prior to the first blood sampling time. In order to maintain patency of the intravenous catheter, the catheter will be flushed with normal saline solution at least hourly. Blood samples will be drawn by venipuncture if the catheter fails. Blood samples will be obtained at t = -0.25 h ± 10 min for the PK analysis of serum strontium, where t = 0 h is the time of study product consumption. Additional blood samples will be collected at all timepoints for backup. Subjects will consume the study product in its entirety within 10 min at t = 0 h. The study product will be dissolved with 100 mL of distilled water with an additional 100 mL of distilled water consumed immediately following. No food will be ingested for the subsequent 2-h period, but *ad libitum* water consumption will be allowed for the remainder of the visit following study product consumption. Water consumption will be recorded at the subsequent test visits. Blood samples will be obtained for the PK analysis of serum strontium at t = 1 and 2 h ± 5 min, where t = 0 h is the start of study product consumption. Subjects will be administered a standard breakfast immediately following the t = 2 h blood draw. Subjects will consume the breakfast meal in its entirety within 30 min.

Blood samples will be obtained via the indwelling venous catheter or venipuncture at t = 3, 4, 5, 6, and 8 h ± 5 min, where t = 0 h is the start of study product consumption, for the PK analysis of serum strontium. Subjects will be administered a standard lunch (immediately following the t = 6 h blood draw), a standard snack (immediately following the t = 8 h blood draw) and a standard dinner (at t = 10 h). Subjects will consume the meals/snack in their entirety within 30 min. Following the final blood draw at t = 12 h ± 5 min, AEs will be assessed. Subjects will be dispensed a blank/new 24-h Diet Record to record all food and beverage consumed the day prior to Visit 3 (day 7); as well as a copy of the completed 24-h Diet Record (from day -1) with instructions to replicate the same food and beverage intake as closely as possible the day prior to the subsequent visit. Study instructions will also be provided [(i.e., fasting compliance (10-14 h, water only) and avoidance of alcohol 3 d prior to the subsequent test visits].

At Visits 3 and 4 (days 7 and 14), subjects will return to the clinic for clinic visit procedures (i.e., vital signs; body weight; review inclusion and exclusion criteria for relevant changes, and concomitant medication/supplement use review). AEs will be

assessed and subjects will be queried about study instructions compliance. The 24-h Diet Record will be collected and study staff will review the 24-h Diet Record to compare food and beverage consumption to the day -1 recall for consistency. If the subject's food intake is not consistent from the 24-h Diet Record reviewed at Visit 2 (day 0), the study staff should contact the Project Manager before continuing the visit as the test visit may require rescheduling. Subjects will then crossover to the next sequential dose of study product [medium dose at Visit 3 (day 7) and high dose at Visit 4 (day 14)] and repeat the PK test described above for Visit 2.

5.3 Flowchart

	Screening	Test Days		
		Low Dose	Medium Dose	High Dose
Visit[1]	**1**	**2**	**3**	**4**
Days	**-7**	**0**	**7**	**14**
Informed Consent/HIPAA[2]	X			
Clinic Visit[3]	X	X	X	X
Medical History	X			
Chemistry Profile[4]	X			
Hematology Panel[5]	X			
In-clinic Urine Pregnancy Test[6]	X			
Vein Access Scale Assessment[7]	X			
Study Instructions/Query[8]	X	X	X	X
Enrollment		X		
Capillary Glucose[9]	X	X	X	X
Dispense 24-h Diet Record[10]	X	X	X	
Collect/Review/Copy 24-h Diet Record[11]		X	X	X
Pharmacokinetic Test[12]		X	X	X
Backup Blood Samples[13]		X	X	X
Adverse Event Assessment[14]		X	X	X

Footnotes:

[1] A period up to 21 d will be allowed between Visits 1 and 2 (days -7 to 0) and the washout period between Visits 2 and 3 (days 0 and 7) and Visits 3 and 4 (days 7 and 14) will be 6-13 d.

[2] Health Insurance Portability and Accountability Act (HIPAA) for disclosure of protected health information. Signed document authorizes the use and disclosure of the subject's Protected Health Information by the Investigator and by those persons who need that information for the purposes of the study.

[3]Clinic visit procedures include measurement of height (Visit 1 only), body weight, BMI (first visit only), vital signs, and where appropriate, a review of inclusion/exclusion criteria (for eligibility at Visit 1 and for potential protocol deviations at subsequent visits), and concomitant medication/supplement use.

[4]The following will be performed as part of the fasting (10-14 h) chemistry profile: albumin, alkaline phosphatase, total bilirubin, direct bilirubin, calcium, chloride, creatinine, blood urea

nitrogen (BUN), potassium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, total protein, carbon dioxide (CO_2), osmolality, and glucose.

[5]The following will be performed as part of the fasting (10-14 h) hematology panel: white blood cell count (WBC), red blood cell count (RBC), hemoglobin concentration, hematocrit (as volume percent), mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelet count.

[6] To be completed on all women <60 years of age.

[7]Appendix 2.

[8] Subjects will be instructed to fast for 10-14 h and to avoid of alcohol 3 d prior to test visits. Subjects will be queried about compliance with these instructions.

[9]Capillary glucose concentrations will be measured at each clinic visit using an FDA-approved glucometer to ensure adequate fasting (10-14 h). Visits may be rescheduled for non-compliance, in the judgment of the Clinical Investigator.

[10]Subjects will complete a 24-h Diet Record identifying all food and beverages consumed the day prior to Visit 2 (day 0; Appendix 3). A clean copy of the 24-h Diet Record will also be provided with instructions for subjects to complete the record the day prior to Visits 3 and 4.

[11]A copy of the 24-h Diet Record captured the day prior to Visit 2 (day 0) will be given to subjects with instructions to replicate the food and beverage selections to the best of their abilities

[12]Subjects will arrive at the clinic following an overnight fast (10-14 h). Blood samples will be obtained for the PK analysis of serum strontium at t = -0.25 h ± 10 min and 1, 2, 3, 4, 5, 6, 8, and 12 h (± 5 min) where t = 0 h is the time of study product consumption. The study product will be dissolved with 100 mL of distilled water with an additional 100 mL of distilled water consumed immediately following. No food will be ingested for the subsequent 2-h period, but *ad libitum* water consumption will be allowed for the remainder of visit following study product consumption. Water consumption will be recorded at the subsequent test visits. A self-selected standard breakfast (immediately following the t = 2 h blood draw), lunch (immediately following the t = 6 h blood draw), snack (immediately following the t = 8 h blood draw), and dinner (at t = 10 h) will be administered. The study product at Visits 3 and 4 (days 7 and 14) will be administered within ± 30 min of the t = 0 h time established at Visit 2 and the meals will be replicated (Appendix 4).

[13]Backup aliquots of serum will be collected and stored for each timepoint.

[14]Inquiring about AEs will occur with an open-ended question at the beginning and end of study visits.

5.4 Study Sample

Each subject must meet all of the following inclusion criteria and none of the exclusion criteria at baseline (Visit 2, day 0) in order to participate in this study.

5.4.1 Inclusion Criteria

1. Subject is a generally healthy male or female, 18-65 years of age, inclusive.
2. Subject has a score of 7 to 10 on the Vein Access Scale at Visit 1 (day -7).
3. Subjects exhibits a body weight >60 kg and has a BMI of ≥18.0 and <32.0 kg/m^2 at Visit 1 (day -7).
4. Subject is willing to avoid use of any over-the-counter medications and/or dietary supplements (vitamins, minerals and/or other supplements) within 3 d prior to visit 1 (day -7) and/or prescription medications (except for stable-dose oral contraceptives) within 14 d prior to visit 1 (day -7) and throughout the study period.
5. Subject is willing to avoid alcohol 3 d prior to each test visit (Visits 2, 3, and 4; days 0, 7, and 14).
6. Subject is willing to avoid grapefruit and/or grapefruit juice 3 d prior to each test visit (Visits 2, 3, and 4; days 0, 7, and 14).
7. Subject is willing to maintain habitual diet, physical activity patterns, and body weight throughout the trial.
8. Subject is a non-user of all tobacco, smoking products (including, but not limited to cigarettes, cigars, chewing tobacco, e-cigarettes), and nicotine products (e.g., nicotine gum and/or nicotine patches) within 6 months of Visit 1 (day -7) and has no plans to change status during the study period.
9. Subject has no health conditions that would prevent him/her from fulfilling the study requirements as judged by the Clinical Investigator on the basis of medical history and routine laboratory test results.
10. Subject understands the study procedures and signs forms providing informed consent to participate in the study and authorizes the release of relevant protected health information to the Clinical Investigator.

5.4.2 Exclusion Criteria

1. Subject has abnormal laboratory test results of clinical significance at Visit 1 (day -7) at the discretion of the Investigator. One re-test will be allowed on a separate day prior to Visit 2 (day 0), for subjects with abnormal laboratory test results.
2. Subject has a known allergy or sensitivity to any of the ingredients in the study products and/or any ingredients of the meals provided.
3. Subject has a history of anaphylaxis, a documented hypersensitivity reaction, and/or a clinically important reaction to any drug.
4. Subject has a history or presence of clinically important endocrine (including hyperparathyroidism, type 1 or 2 diabetes mellitus and/or hypoglycemia), cardiovascular (including, but not limited to history of myocardial infarction, peripheral arterial disease, stroke), pulmonary (including uncontrolled asthma), hepatic, renal, hematologic, immunologic, dermatologic, neurologic (such as Alzheimer's or Parkinson's patients), rheumatic (including gout), biliary, and/or psychiatric disorders (including depression and/or anxiety disorders), that, in the opinion of the Investigator, could interfere with the interpretation of the study results.

5. Subject has had a loss of 400 mL of blood (e.g., blood/plasma donation) during the prior 30 d of visit 2 (day 0).
6. Subject has a history or current GI disorder that, in the judgment of the Investigator, may have the potential to disrupt normal digestion and absorption.
7. Subject has a history or presence of cancer in the prior two years, except for non-melanoma skin cancer.
8. Subject has a history of bariatric surgery for weight reducing purposes.
9. Subject has recently (within 6 months prior to Visit 1; day -7) had a weight loss or gain >4.5 kg.
10. Subject has uncontrolled hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg) as defined by the blood pressure measured at Visit 1 (day -7). One re-test will be allowed on a separate day prior to Visit 2 (day 0), for subjects with abnormal blood pressure.
11. Subject has extreme dietary habits (e.g., Atkins diet, very high protein, vegetarian, intentional consumption of a high fiber diet), in the opinion of the Clinical Investigator.
12. Subject is a female, who is pregnant, planning to be pregnant during the study period, lactating, or is of childbearing potential and is unwilling to commit to the use of a medically approved form of contraception throughout the study period. The method of contraception must be recorded in the source documentation.
13. Subject has been exposed to any non-registered drug product within 30 d prior to visit 1 (day -7).
14. Subject has a recent history of (within 12 months of screening; Visit 1; day -7) or strong potential for alcohol or substance abuse. Alcohol abuse is defined as >14 drinks per week (1 drink = 12 oz beer, 5 oz wine, or 1½ oz distilled spirits).
15. Individual has a condition the Clinical Investigator believes would interfere with his or her ability to provide informed consent, comply with the study protocol, which might confound the interpretation of the study results, or put the subject at undue risk.

5.4.3 Excluded Medications/Products and Foods

Subjects will be asked to refrain from consuming all over-the-counter medications and dietary supplements (vitamins, minerals and/or other supplements) within 3 d prior to visit 1 (day -7) and/or prescription medications (except for stable-dose oral contraceptives) within 14 d prior to visit 1 (day -7) and throughout the study period. For females on oral contraceptives, the subject must be on a stable dose of oral contraceptives (defined as same dose for the past 90 d prior to Visit 1; day -7). Additionally, subjects will avoid grapefruit and/or grapefruit juice within 3 d of all test visits (Visits 2, 3, and 4; days 0, 7, and 14). Should a subject require any of these medications or supplements, the study staff should consult with the Project Manager to discuss the subject's continued participation in the trial.

5.4.4 Enrollment

If a subject meets all inclusion and none of the exclusion criteria, a staff member will select the next sequential enrollment number for the subject. The enrollment number will

be recorded with the subject's source documentation. The total sample population will include 50% women with the goal of completing a minimum of 6 subjects.

5.5 Study Products

5.5.1 Description

- Low dose (170 mg Sr) strontium *L*-lactate
- Medium dose (340 mg Sr) strontium *L* -lactate
- High dose (680 mg Sr) strontium *L* -lactate

The study product will be provided as a dry powder packaged in individual vials. The study product will be prepared for consumption by dissolving the dry powder in the vial by adding 10 mL of distilled water and stirring the mixture. This liquid mixture will then be poured into an administration cup. An additional 10 mL of distilled water will be used to rinse the remaining study product into the administration cup. The remaining 80 mL of distilled water will be added directly into the administration cup. Following subject consumption of the 100 mL distilled water (with dissolved study product powder), another 100 mL will be added into the administration cup, swirled, and consumed by the subject. Study product information may be found in Appendix 5.

5.5.2 Labeling and Packaging

The Sponsor will provide pre-packaged, sealed, study product, each item labeled with the protocol number, dose, expiration date, and the statement "For Investigational Use Only."

5.5.3 Storage and Dispensing

Study products will be stored in a cool, dry, secure location at ambient temperature. Study product supplies are to be used only in accordance with this protocol and under the supervision of the Clinical Investigator. All records must be available for inspection by the Sponsor and are subject to regulatory agency inspection at any time. Copies of the records will be provided to the Sponsor at the conclusion of the study. A written explanation from the study staff will be required for any missing study product.

5.6 Clinical Measurements

5.6.1 Clinic Visit Procedures

Clinic visits will include assessment of height (Visit 1; day -7 only), body weight (Visits 1 through 4; days -7 to 14), BMI (Visit 1; day -7 only), evaluation of prior and concomitant medication/supplement use, and a review of inclusion/exclusion criteria (for eligibility at Visit 1 and for potential protocol deviations at subsequent visits).

Standardized vital signs measurements will be assessed at each clinic visit (Visits 1 through 4; days -7 to 14) and will include resting blood pressure and heart rate measured using an automated blood pressure measurement device. Blood pressure will be obtained after the subject has been sitting for at least five min. Systolic and diastolic pressures will be measured once using an appropriate sized cuff (bladder within the cuff must encircle ≥80% of the arm). Clinic staff may take a second blood pressure and heart rate,

if warranted. In the event a second measure is assessed; the second measurement will be recorded in the eCRF. Should elevated blood pressure be present at the screening visit (Visit 1; day -7), one retest will be allowed on a separate day, prior to Visit 2 (day 0).

5.6.2 Laboratory Measurements

The procedures for all clinical laboratory measurements will be outlined in a laboratory instruction sheet. Laboratory parameters that are missing or have not been obtained must be entered in the eCRF as "not done."

The FDA-approved glucometer, with test strips from the same lot, will be used for determination of the in-clinic (Biofortis Clinical Research, Addison, IL) fasting capillary blood glucose (mmol/L) at Visits 1, 2, 3, and 4 (days -7, 0, 7, and 14) to ensure adequate fasting (10-14 h). Visits may be rescheduled for non-compliance, in the judgment of the Clinical Investigator.

The following will be performed as a part of the fasting (10-14 h) chemistry profile at Visit 1 (day -7): glucose, sodium, potassium, chloride, carbon dioxide, BUN, creatinine, calcium, osmolality, AST, ALT, ALP, total bilirubin, total protein, and albumin. Analytes will be assessed by Elmhurst Memorial Reference Laboratory (Elmhurst, IL).

The following will be performed as part of the fasting (10-14 h) hematology measurements at Visit 1 (day -14): WBC, RBC, hemoglobin concentration, hematocrit (as volume percent), MCV, MCH, MCHC, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelet count. Analytes will be assessed by Elmhurst Memorial Reference Laboratory (Elmhurst, IL).

Blood samples for the PK analysis of serum strontium will be collected at Visits 2, 3 and 4 (days 0, 7, and 14) at t = -0.25 h (± 10 min) and t = 1, 2, 3, 4, 5, 6, 8, 10, and 12 h (± 5 min), where t = 0 h is the start of study product consumption. Analytes will be assessed by NMS Labs (Willow Grove, PA). Additional samples will be stored as backup in the event the original sample is not viable.

An in-clinic urine pregnancy test will be performed on all women <60 years of age at Visit 1 (day -7).

5.6.3 Vein Access Scale Assessment

At Visit 1 (day -7), study staff will complete the Vein Access Scale assessment to evaluate if the subject is a good candidate for the placement of the venous indwelling catheter. A score of seven to 10 is inclusive (Appendix 2).

5.6.4 Study Instructions/Query

Subjects will receive the following study instructions: fasting compliance (10-14 h, water only) and avoidance of alcohol 3 d prior to test visits (Visits 2, 3, and 4; days 0, 7, and 14]. Subjects will be queried about compliance with these instructions at Visits 2, 3, and 4 (days 0, 7, and 14).

5.6.5 24-h Record/Dispense Copy of 24-h Diet Record

Subjects will complete a 24-h Diet Record (Appendix 3) the day prior to Visit 2 (day 0). All foods and beverages consumed are to be recorded in the 24-h Diet Record. Subjects will be instructed to replicate the same diet intake the 24 h prior to Visits 3 and 4 (days 7 and 14). At the beginning of Visits 3 and 4 (days 7 and 14), a study staff member will review each subject's 24-h Diet Record completed prior to the visit and compare the food consumption to the first 24-h Diet Record (reviewed at Visit 2; day 0) for consistency. If the subject's food intake is not consistent with intake from the day prior to Visit 2, study staff should contact the Project Manager before continuing the visit. The test visit may be rescheduled at the discretion of the Biofortis Scientific Advisor or designee.

5.6.6 Pharmacokinetic Testing

A PK test will be initiated at Visit 2 (day 0). Subjects will be queried to confirm compliance with study instructions. If a subject fails to comply, the subject may be asked to reschedule the test day.

At Visit 2 (day 0), eligible subjects will arrive at the clinic fasted (10-14 h); after clinic visit procedures the PK test will begin with the insertion of an intravenous catheter at least 5 min prior to the first blood sampling time. In order to maintain patency of the intravenous catheter, the catheter will be flushed with 10 mL normal saline solution at least hourly. Should the catheter fail, blood samples will be drawn by venipuncture. Blood samples will be obtained at t = -0.25 h ± 10 min for the PK analysis of serum strontium followed by study product administration at t = 0 h. The study product will be dissolved with 100 mL of distilled water with an additional 100 mL of distilled water consumed immediately following. No food will be ingested for the subsequent 2-h period, but *ad libitum* water consumption will be allowed for remainder of visit following study product consumption. Water consumption will be recorded at the subsequent test visits. Blood samples will be obtained for the PK analysis of serum strontium at t = 1 and 2 h ± 5 min, where t = 0 h is the start of study product consumption. Subjects will be administered a standard breakfast immediately following the t = 2 h blood draw. Subjects will consume the breakfast meal in its entirety within 30 min.

Blood samples will be obtained via the indwelling venous catheter or venipuncture at t = 3, 4, 5, 6, and 8 h ± 5 min, where t = 0 h is the start of study product consumption, for the PK analysis of serum strontium. Subjects will be administered a standard lunch (immediately following the t = 6 h blood draw), a standard snack (immediately following the t = 8 h blood draw), and a standard dinner (at t = 10 h). Subjects will consume the meals/snack in their entirety within 30 min. The final blood draw will be obtained at t = 12 h ± 5 min. The study product at Visits 3 and 4 (days 7 and 14) will be administered within ± 30 min of the t = 0 h time established at Visit 2 (day 0) and the meals/snack will be replicated.

Pharmacokinetic Test Day Schedule

Test time (t = "x" h)	Visits 2, 3, and 4 (days 0, 7, and 14)
t = -1.0 h	• Arrive at clinic; • Study instructions query; • Clinic visit procedures (vitals and body weight); • Enrollment (Visit 2; day 0 only); • AE assessment; • IV inserted (at least 5 min prior to first blood draw)
t = -0.25 h ± 10 min	• Blood sample obtained; • Additional sample stored
t = 0 h	• Administer assigned study product; • *Ad libitum* water consumption allowed for remainder of visit
t = 1 and 2 h ± 5 min	• Blood sample obtained; • Additional sample stored
Immediately following the t = 2 h blood draw	• Administer standard breakfast (consumed in 30 min); •
t = 3, 4, 5, and 6 h ± 5 min	• Blood sample obtained; • Additional sample stored
Immediately following the t = 6 h blood draw	• Administer standard lunch (consumed in 30 min)
t = 8 h ± 5 min	• Blood sample obtained; • Additional sample stored
Immediately following the t = 8 h blood draw	• Administer standard snack (consumed in 30 min)
t = 10 h ± 5 min	• Administer standard dinner (consumed in 30 min)
t = 12 h ± 5 min	• Blood sample obtained; • Additional sample stored; • AE assessment (immediately upon completion of blood sampling); • Review study instructions; dispense copy and blank 24-h Diet Record (Visit 2 and 3 only)

5.7 Procedures at Each Clinic Visit

Procedures listed are not necessarily performed in the order below.

5.7.1 Screening (Visit 1; day -7)

- Informed consent/HIPAA
- Medical history
- Clinic visit
  - Height
  - Body weight
  - BMI assessment

    - Vital signs
    - Assess concomitant medication/supplement use
    - Review inclusion/exclusion criteria
- Vein Access Scale
- Chemistry profile
- Hematology panel
- Capillary glucose
- In-clinic urine pregnancy test, where applicable
- Dispense 24-h Diet Record
- Review study instructions

5.7.2 Test Visits (Visits 2, 3, and 4; days 0, 7, and 14)

- Clinic visit
    - Body weight
    - Vital signs
    - Assess concomitant medication/supplement use
    - Review inclusion/exclusion criteria
- Study instruction query
- Collect/review 24-h Diet Record
- Assess AEs
- Capillary glucose
- Enrollment (Visit 2, day 0 only)
- PK Test
- Assess AEs
- Dispense copy (from day -1) of 24-h Diet Record (Visits 2 and 3; days 0 and 7 only)
- Dispense blank 24-h Diet Record (Visits 2 and 3; days 0 and 7 only)
- Review study instructions (Visits 2 and 3; days 0 and 7 only)

5.8 Early Termination Procedures

The term "Early Termination" refers to a subject's non-completion of the study. Should a subject decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. In the event that a subject is withdrawn from the study, the reason for the withdrawal and the party who initiated the withdrawal (subject or Clinical Investigator) will be documented. Should the subject decide to withdraw, documentation of early termination and any AEs and concomitant medication use should be recorded.

The primary reason for a subject withdrawing prematurely should be selected from the following standard categories:

Adverse Event – event which results in discontinuation of the study product by the subject or that in the judgment of the Clinical Investigator for the best interest of the

subject requires discontinuation of study product (includes all categories of study product relatedness; Not Related, Unlikely, Possibly, Probably, and Definitely).

Death – death of the subject.

Withdrawal of Consent – subject desires to withdraw from further participation in the study in the absence of a medical need to withdraw determined by the Clinical Investigator.

Lost to Follow-Up – subject did not return for one or more follow-up visit(s) following dispensing of study product and could not be contacted thereafter. The reason for withdrawal was unknown and could not be documented.

Other – causes of premature termination from the study other than the above, such as theft or loss of study products, termination of study by Sponsor, etc.

6. Data Analysis and Statistical Methods

6.1 Outcome Variables

The outcome variables will include the following parameters for serum strontium at all three doses:

- Incremental area under the curve (iAUC) for serum strontium from pre-product consumption (t = -0.25 h) to 12 h ($iAUC_{-0.25-12h}$)
- iAUC for serum strontium from pre-product consumption (t = -0.25 h) to infinity ($AUC_{0-\infty}$)
- Maximum plasma concentration (Cmax)
- Time to Cmax (Tmax)
- Rate of elimination (λ_z)
- Half life ($t_{1/2}$)
- Estimated fraction of the dose which is absorbed

6.2 Sample Size

No formal sample size formulation was performed. As requested by sponsor, a total of 10 subjects (approximately equal distribution of sex) will be enrolled with the goal of completing a minimum of 6 subjects.

6.3 Statistical Analysis

All statistical analyses will be conducted using SAS for Windows (version 9.2, or higher, Cary, NC) and/or R 3.3.1 (R Core Team 2016). The data will be analyzed for the modified intent-to-treat population, which will include all subjects who complete all test visits. Subject data may also be excluded for the following reasons and possibly others:

- Non-compliance by the subject, including, but not limited to:

- Missing appointments
- Use of prohibited drugs or any products thought to alter the outcome variables during the study
- Not adhering to instructions as outlined in the protocol

All decisions regarding subject population and data inclusion will be documented prior to database lock.

6.4 Baseline Characteristics

Descriptive statistics [number of subjects, mean, standard error of the mean (SEM), median, interquartile limits, minimum and maximum or frequency counts] will be presented for subject demographics and anthropometric measurements collected at screening/baseline.

6.5 Outcome Analysis

Descriptive statistics (i.e. number of subjects, minimum and maximum, median, inter-quartile limits, mean, and SEM) will be presented for all the continuous outcomes for each dose level.

6.6 Safety Analysis

Safety will be assessed by AEs reported by subjects, as well as assessment of vital signs and body weight.

6.7 Missing or Incomplete Data

Missing data will not be imputed and only observed data will be included in the analysis.

7. Study Monitoring

7.1 Concomitant Medication/Supplements and Treatment

All concomitant medications/supplements used 30 d prior to Visit 1 (day -7) and during the study will be reported to the study personnel for assessment and recorded in the subject's eCRF.

Use of the medications/supplements described in the "Exclusion Criteria" section and Appendix 1 is not allowed during this study. If a subject requires any of these medications/supplements, the subject may not enter the study. If a subject uses any exclusionary medications/supplements once enrolled, a protocol deviation will be documented.

7.2 Compliance Monitoring

Compliance with the study product will be recorded in the subject's source document. Non-compliance will be witnessed by study staff and defined as not consuming the study product in its entirety at Visits 2, 3, and 4 (days 0, 7, and 14).

7.3 Adverse Event Monitoring

In a consensus view of guidelines for the design, conduct and reporting of human intervention studies to evaluate the health benefits of foods, an International Life Sciences Institute Europe Expert Group defines an AE as "*any untoward medical occurrence or undesirable clinical experience in a participant in a clinical trial, whether or not considered related to the intervention*" (Welch 2011). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures (including laboratory test abnormalities where applicable). Therefore, clinical observations, including responses to the question, "Have there been in any changes in your health or medications since you were last asked?" will be collected at Visits 2 through 4. These observations will be reviewed for assessment of AE, including severity and potential relationship to the intervention as determined by the Clinical Investigator.

Events should be considered AEs if they:

- Result in discontinuation from the study,
- Require treatment or any other therapeutic intervention,
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality),
- Are associated with clinical signs or symptoms judged by the Clinical Investigator to have a significant clinical impact.

7.3.1 Grading and Severity

The Clinical Investigator will evaluate all AEs with respect to their severity, and record the outcome and action taken on the AE eCRF. AEs will be graded as:

Mild:	Awareness of symptoms but easily tolerated
Moderate:	Discomfort enough to interfere with but not prevent daily activity
Severe:	Unable to perform usual activity

7.3.2 Relationship

The Clinical Investigator will also judge the likelihood that the AE was related to the study product and document this on the appropriate eCRF as:

NOT RELATED	This category applies to those adverse experiences which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
UNLIKELY	In general, this category can be considered applicable to those experiences that after careful medical consideration at the time they are evaluated, are judged to be, unlikely related to the study product administered.
POSSIBLY	This category applies to those adverse experiences for which, after careful medical consideration at the time they are evaluated, a connection with the study product administration appears possible but cannot be ruled out with certainty.
PROBABLY	This category applies to those adverse experiences that, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study product.
DEFINITELY	This category applies to those adverse experiences which, the Clinical Investigator feels are incontrovertibly related to the study product.

Appropriate therapeutic action and follow-up measures will be performed by the Clinical Investigator in accordance with good medical practice.

7.3.3 Serious Adverse Event Definition/Qualification

A SAE is defined as an AE that results in any of the following outcomes:

- Death (note that death is the outcome of a SAE and the cause of death should be listed as the AE)
- Life-threatening event
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- Congenital anomaly or birth defect
- Any other important medical event that may not result in death, be life-threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

In the event of a SAE, the subject may be dropped from the study if the Clinical Investigator deems it necessary.

7.3.4 Serious Adverse Event Reporting Instructions

If in the opinion of the Clinical Investigator the event meets the criteria of a SAE the following procedures will be followed:

- The Clinical Investigator will report the SAE to Biofortis Innovation Services immediately upon becoming aware of the event.

- In addition, the initial SAE report should be submitted with other applicable information (such as medical history, concomitant medications, AEs) to Biofortis Innovation Services within 24 h of reporting the event to the attention of:

  Kristen Sanoshy
  Project Manager
  Biofortis Innovation Services
  211 East Lake Street
  Addison, IL 60101
  Tel: (630) 516-3990
  E-mail: Kristen.Sanoshy@mxns.com

- The Biofortis Scientific Advisor

  Eunice Mah, Ph.D.
  Senior Scientist
  Biofortis Innovation Services
  211 East Lake Street
  Addison, IL 60101
  Tel: (740) 590-1871
  Email: Eunice.Mah@mxns.com

- The Clinical Investigator will also notify the Institutional Review Board (IRB) of the event within the parameters and timeframe specified under the IRB Standard Operating Procedures (SOP) after becoming aware of the SAE. An initial report followed promptly by a complete report will be forwarded to the IRB.
- Follow-up information relating to a SAE must be submitted to Biofortis Innovation Services as soon as additional data related to the event are available.
- If a subject is hospitalized or hospitalization is prolonged due to the SAE, the hospital discharge summary will be obtained if possible when it becomes available.
- If a death occurs and an autopsy is performed, a copy of the autopsy report will be obtained if possible when it becomes available. All efforts must be undertaken to obtain follow-up information promptly.

7.3.5 Electronic CRF Recording of Adverse Events

All AEs will be recorded on the AE eCRF page. For subjects who have an ongoing AE at their final study visit, a follow-up AE eCRF page will be completed after 30 d. All SAEs must be recorded on the AE and SAE eCRF page.

7.3.6 Serious Adverse Event Follow-Up

For all ongoing SAEs occurring during the study, the Clinical Investigator must submit follow-up reports to Biofortis Innovation Services regarding the subject's subsequent course. All SAEs that are ongoing at the end of the study or upon discontinuation of the subject's participation must be followed until either:

- The event resolves, or
- The event/condition has stabilized (e.g., in the case of persistent impairment), or
- The event returns to baseline, if a baseline value is available, or
- The subject dies, or
- The event can be attributed to other than the study treatment, or to other than the study conduct.

7.3.7 Pregnancy

There are no adequate and well-controlled studies on strontium *L*-lactate use in pregnant women, therefore, pregnant or lactating women will be excluded from the study. Additionally, the outcome variables measured would be expected to be affected by pregnancy and lactation. All female participants <60 years of age will undergo in-clinic urine pregnancy testing at Visit 1 (day -7). Pregnant or lactating women will be excluded from the study and women of childbearing potential will be required to use appropriate contraceptive methods to avoid pregnancy. Documentation of contraception method must be recorded in the source chart.

Although pregnancy is not a SAE, all pregnancies occurring in enrolled subjects will be reported within 24 h of notification. The Clinical Investigator will immediately notify the Sponsor, the Project Manager and the IRB about the pregnancy. Should a female subject become pregnant at any time after randomization the Clinical Investigator will be required to follow the subject through the pregnancy term and report to Biofortis Innovation Services the course of the pregnancy including perinatal and neonatal outcomes.

8. Conduct of the Study

8.1 Ethics and Regulatory Considerations

This study will be conducted according to Good Clinical Practice Guidelines, the Declaration of Helsinki (2000), and US 21 CFR. Signed written informed consent for participation in the study will be obtained from all subjects before protocol-specific procedures are carried out. Subjects will be informed of their right to withdraw from the study at any time.

8.2 Institutional Review Board

The Clinical Investigator will ensure that an appropriately constituted IRB, in compliance with the requirements of 21 CFR 56, reviews and approves the clinical study. Before the study is started, the Clinical Investigator will forward copies of the protocol and consent form for this study to the IRB for review and approval. IRB approval must refer to the study by exact protocol title and number, identify the documents reviewed, and state the date of review. The IRB must be informed of all subsequent protocol amendments. No alterations, modifications to IRB-approved documents, including the protocol, protocol summary, consent form, recruitment materials and questionnaires will be allowed. The IRB must also be informed of all SAEs and of unexpected AEs as outlined in the IRB's

SOPs or reporting guidelines. In addition, the Clinical Investigator will immediately forward copies of all correspondence with the IRB to Biofortis Innovation Services.

8.3 Informed Consent and Protected Health Information

The study will be explained verbally as well as on the informed consent document. Each subject will be given ample opportunity to inquire about details of the study and to read and understand the consent form before signing it.

Consent must be documented by the dated signature of the subject. Each subject's signed informed consent document must be kept on file by the Clinical Investigator for possible inspection by regulatory authorities or by the Sponsor. The subject should receive a copy of the written informed consent document once he/she has signed it.

The Sponsor recognizes the importance of protecting the privacy of subject data. Therefore, for study sites within the United States, the informed consent form will incorporate, or be accompanied by, a separate document incorporating HIPAA-compliant wording, by which subjects authorize the use and disclosure of their Protected Health Information by the Clinical Investigator and by those persons who need that information for the purposes of this study.

A subject may not be admitted to the study unless informed consent of the subject (or his/her legally authorized representative) has been obtained.

8.4 Subject Confidentiality

The Clinical Investigator is responsible for ensuring that subjects' anonymity will be maintained. Electronic CRFs or other documents will identify subjects by initials, number, or code, and not by name. The Clinical Investigator will keep a separate log showing codes, names, and addresses. All documents showing the subjects' identity will be kept in strict confidence by the Clinical Investigator. However, the Clinical Investigator agrees that the Sponsor, its employees or agents, the IRB, as well as representatives of the FDA, will have the right to audit and review pertinent medical records relating to this clinical trial and that the subjects will provide written informed consent to this effect.

8.5 Withdrawal of Subjects from the Study

Subjects may be removed from the study for any of the following reasons:

- A subject requests discontinuation;
- The Clinical Investigator initiates removal for medical or compliance reasons;
- Occurrence of any AE or condition that could, in the Clinical Investigator's opinion, interfere with the evaluation of the treatment effect of the study product or put the subject at undue risk.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable, therefore, unnecessary withdrawal of subjects should be avoided.

Should a subject decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. In the event that a subject is withdrawn from the study, the reason for the withdrawal will be documented in the eCRF. Prior to a subject's withdrawal from the study, an attempt will be made to conduct an early termination visit, which will include the clinic visit procedures and AE assessment.

9. Administrative Matters

All references to the Sponsor in this section include all designees e.g., Contract Research Organizations or Consultants acting on behalf of the Sponsor.

9.1 Changes to the Protocol

All changes to the protocol must be documented by amendments to the protocol signed by the Sponsor and the Clinical Investigator. The amended protocol and a revised informed consent form will be submitted for approval to the IRB. A copy of the approval will be provided to Biofortis Innovation Services. Where the local IRB regulations regarding protocol amendments differ from this policy, the local regulations will apply.

The above-mentioned requirements do not preclude any immediate action from being taken in the interests of subjects' safety.

9.2 Protocol Deviations and Violations

A protocol deviation is a minor departure from the protocol that is approved by the Project Manager prior to implementation and does not compromise subject safety or the integrity of the data. Any deviation from the inclusion/exclusion criteria requires an approved waiver from the Sponsor or authorized designee prior to randomization in order to enroll that subject into the study. The site should accurately document the deviation and approval in the source document and complete the protocol deviation/violation eCRF.

A protocol violation is a divergence from the IRB-approved protocol that is not approved by the Sponsor or authorized designee prior to implementation. A violation can be classified as major or minor. A major violation compromises the safety of the subject or the integrity of the data collected. A minor violation is a less-significant departure from the protocol that, though not pre-approved, does not compromise the safety of the subject or the integrity of the data collected. The site should accurately document the violation in the source document and complete the Protocol Deviation/Violation eCRF. Violations that could significantly influence subject safety will be reported to the IRB.

9.3 Electronic Case Report Forms

Data collected in the eCRF will be documented in an anonymous fashion (e.g., the subject will be identified only by a study number and their initials). Each evaluation recorded in the eCRF will be performed at the time specified in the protocol.

All information required by the protocol should be documented in the source records and provided in the eCRF. The Clinical Investigator must agree to complete and maintain

source documents for each subject participating in the study. An explanation must be given for any omissions. All eCRFs must be completed as soon as possible after the subject's visit, in order that the monitor may verify the validity and completeness of the data. The Clinical Investigator will review and sign (as required) all eCRFs for completeness and accuracy. All information on the eCRFs must be traceable back to the source documents.

9.4 Clinical Monitoring

An initiation meeting will be conducted by the Sponsor or an approved representative. At this meeting the protocol, eCRFs, and pertinent aspects of the CFR will be reviewed with the Clinical Investigator and all study staff.

Remote and on-site monitoring visits will be conducted during the study, focusing on human participant protection and data integrity risks of the trial. A clinical monitoring plan will be developed which identifies specific risk-based monitoring focal points. These may include:

- Informed consent
- Eligibility criteria
- SAEs
- Serious protocol violations
- Endpoints
- Test article administration
- Accountability

No data disclosing the identity of participants will leave the study center, except as described in Section 10. Biofortis Innovation Services and any designees will maintain confidentiality of all participant records.

The Clinical Investigator must ensure that access to the CRF is secured and that other study documentation is stored in a secure location. During the course of the study, the responsible Biofortis Innovation Services staff will be available to discuss any matters relating to the conduct of the study.

9.5 Auditing Procedures

In addition to the monitoring visits outlined above, an investigational site may undergo a quality assurance audit. The Sponsor representatives or a regulatory agency such as the FDA may conduct the audit. If a regulatory agency requests an audit of the study site, the Clinical Investigator is required to inform the Sponsor and Biofortis Innovation Services immediately.

9.6 Records Retention

All study documentation generated in connection with this study will be retained for at least five years after the last approval of a marketing application in an International Conference on Harmonization (ICH)-region and until there are no pending or contemplated marketing applications in an ICH-region or at least 5 years have elapsed

since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Clinical Investigator/institution as to when these documents no longer need be retained. The study documents include IRB approvals for the study protocol and all amendments, all source documents and laboratory records, eCRF records, signed subject informed consent forms, and any other pertinent study document. The Clinical Investigator agrees to supply Biofortis Innovation Services with a written confirmation that these procedures are in place and will be adhered to.

9.7 Termination of Study

The Sponsor and the Clinical Investigator reserve the right to terminate the study at any time. In terminating the study, the Sponsor and the Clinical Investigator will assure that adequate consideration is given to the protection of each subject's interest.

10. Disclosure

By conducting this study, the Clinical Investigator agrees that all information provided will be maintained by the Clinical Investigator and his/her staff in strict confidence. Such information may be communicated to the Sponsor Scientists/Scientific Committee and/or IRB/Ethics Committee under a similar, appropriate understanding of the confidential nature of the information. Study documents provided (protocols, other material, as necessary) will be stored appropriately to ensure their confidentiality. It is understood that the confidential information provided to the Clinical Investigator will not be disclosed to others without written authorization, except to the extent necessary to obtain informed consent from those subjects who are eligible and choose to participate in the study. Such information will not be provided to potential subjects or subjects by telephone or to any other individual.

11. References

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Slosman DO, Rizzoli R, Pichard C, Donath A, Bonjour JP. Longitudinal measurement of regional and whole body bone mass in young healthy adults. Osteoporos Int. 1994 Jul; 4(4): 185-190.

Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, Dawson-Hughes B. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res. 2014 Nov;29(11):2520-2526.

Appendix 1: Examples of Exclusionary Medications, Supplements, and Foods
This list is not intended to be comprehensive.

CLASS OF DRUG/PRODUCT	GENERIC/BRAND NAME
Excluded within 14 d prior of Visit 1 (day -7) and throughout the study	
Prescription medication	All prescription medications except stable dose oral contraceptives (defined as same dose for the past 90 d prior to Visit 1; day -7)
Excluded within 3 d prior of Visit 1 (day -7) and throughout the study	
Over-the-counter medications	All over-the-counter medications
Dietary supplements	Any dietary supplement (including protein supplements)
Excluded within 3 d prior to each test visit (Visits 2, 3, and 4; days 0, 7, and 14)	
Grapefruit and/or grapefruit juice Alcohol	

Appendix 2: Vein Access Scale

Subject Initials: _____ **Screen #:** _____

Date: _____

RATING (circle one)	APPEARANCE
10	Four or more large, sturdy, well anchored veins or two giant veins that are good with many alternative sites
9	Three or more large, sturdy, well-anchored veins or one giant vein that is good with many alternative sites
8	Two or more large, sturdy, well-anchored veins with alternative sites
7	One large, sturdy, well-anchored vein with alternative sites
	Anything below this line is exclusionary
6	Two draw sites with questionable stability with possible alternatives. (Including rolling veins, etc.)
5	One draw site with questionable stability with possible alternatives
≤ 4	One questionable draw site and alternatives. Other factors to consider: number of sticks required for screening draw; quality and skill level of drawer(s)

Evaluator's Initials:_____

Appendix 3: 24-h Diet Record

Protocol #: 1703	
Dates Recorded:	
Date of Visit Dispensed:	Visit No. Dispensed:
Date of Visit Collected:	Visit No. Collected:

For Office Use Only

Subject Initials:	
Screen Number:	
Staff name:	
Site #:	Date Sent:

Please provide any information that affects the interpretation and analysis of this diary:

General Instructions

1. Print **LEGIBLY** in blue or black ink.
2. Record each meal **IMMEDIATELY** after it is eaten.
3. In the **PLACE** column, use **H** for meals eaten at **HOME** or list name of restaurant if eaten at restaurant (including fast food).
4. In the **MEAL** column, use the following codes to indicate the meal eaten:
   B = Breakfast
   L = Lunch
   D = Dinner/Supper
   S = Snack
   BR = Brunch
5. Leave 2 or 3 **BLANK** lines between meals.

How to Keep an Accurate Diet Record

1. Please keep a record of **EVERYTHING** you eat or drink for the day advised by your study coordinator.
2. Record **BRAND NAMES** for any foods eaten whenever possible. Include any modifications of the food item.

Examples: low-sodium, fat-free, artificial sweetener.

3. Be specific in recording **PORTION SIZES** eaten.
   - Use standard household measurements: tbsp, tsp, cup, ounces or number of pieces.
   - Use dimensions: length x width x depth.
4. List **INGREDIENTS** and amounts for recipes and mixed dishes. Include a food label or recipe when available.
5. Please remember to include any condiments, sweeteners or anything else you add to food while cooking or eating (example mustard or ketchup).

Checking Your Diet Record

Before you come to your visit, use the check list below to assure you have provided enough details about your foods.

Meat:

- ❑ What cuts of meat were eaten?
- ❑ Was the fat trimmed off before cooking?
- ❑ How was the meat prepared?
- ❑ Was the poultry skin eaten or removed (before or after cooking)?

Dairy:

- ❑ What type of cheese was used?
- ❑ What kind of milk was consumed or used during cooking?
- ❑ Was the yogurt, pudding, or ice cream made from nonfat, low-fat or whole milk ingredients?

Fats and Oils:

- ❑ Were fats or oils used in cooking or baking?
- ❑ What brand of margarine, butter or oil was used?
- ❑ What type of margarine, butter or oil was used (tub, stick, liquid)?
- ❑ Was salad dressing or mayonnaise used?

Salt:

- ❑ Was salt added in cooking or at the table?

Subject Initials: _____ **Screen #:** _____

Date of Diary: 6/14/16 Day of the Week: S M (T) W Th F Sa

Home or Restaurant name	TIME	MEAL	Food and Beverages Give Specific Details (one food item per line) Include spices, sweeteners, condiments, etc.	AMOUNT and/or DIMENSIONS	COOKING METHOD	TYPE OF FAT USED	REVIEWERS COMMENTS (Do not write here)
home	7:30 A	B	Life cereal	1 cup			
home	7:30 A	B	1% milk (not fortified)	1 cup			
home	7:30 A	B	decaf Folgers coffee	8 oz			
Jimmy John's	11:30 A	L	Turkey sandwich (Turkey Tom)	1 serving		Light Mayo	Note: Removed tomatoes
Jimmy John's	11:30 A	L	Jumbo kosher dill pickle				
Jimmy John's	11:30 A	L	Large diet Coke	32 oz			
home	2:00 P	S	apple	medium			
Denny's	4:30 P	D	rice	6 oz	Boiled		
Denny's	4:30 P	D	Grilled chicken breast	1 breast	Grilled	butter	
Denny's	4:30 P	D	decaf coffee	8 oz			
Denny's	4:30 P	D	sugar	1 packet			
home	7:00 P	S	Jay's pretzels	8 pretzels			
home	all day		water	32 oz			

Subject Initials: _____ **Screen #:** _____

Date of Diary: _____ Day of the Week: S M T W Th F Sa

Home or Restaurant name	TIME	MEAL	Food and Beverages Give Specific Details (one food item per line) Include spices, sweeteners, condiments, etc.	AMOUNT and/or DIMENSIONS	COOKING METHOD	TYPE OF FAT USED	REVIEWERS COMMENTS (Do not write here)

Appendix 4: Sample Test Day Meals

Sample breakfast meal

Food item	Serving Size
Thomas' Plain Bagel	1 or 2 full bagels
Butter	2 to 4 pats
Chobani Lowfat Greek Yogurt, any flavor	6 oz
Sargento Mozzarella String Cheese	1 or 2 pieces
Coffee, Tea, Diet Soda, or Water	12 oz.
Creamer and/or Sweetener	As desired

Sample lunch meal

Food item	Serving Size
Smart Ones Slow Roasted Turkey Breast	1 or 2 entrees
Baby Carrots	80 g
Yoplait Yogurt, Lowfat, Peach, Strawberry, or Vanilla	1 container
Mott's Apple Sauce	1 or 2 individual cup
Quaker Lowfat Oatmeal Raisin Bar	1 or 2 packages
Coffee, Tea, Diet Soda, or Water	12 oz.
Creamer and/or Sweetener	As desired

Sample snack

Food item	Serving Size
Special K Pastry Bar	1 or 2 packages
Chocolate pudding cup	1 or 2 individual cup
Small apple or banana	1 or 2

Sample dinner meal

Food item	Serving Size
Jimmy Johns Pepe (Ham & Cheese; #1) Big John (Roast Beef; #2), or Turkey Tom (Turkey; #4)	1 sandwich
Jimmy Chips	1 bag
Dole Fruit Bowls Mixed Fruit in 100% Juice	1 individual cup
Nabisco Chips Ahoy	1- 4 cookie package
Coffee, Tea, Diet Soda, or Water	12 oz.
Creamer and/or Sweetener	As desired

Appendix 5: Study Product Information

Each study product dose will be provided in one vial. Each vial will be filled to contain the desired amount of the strontium *L*-lactate.

Low Dose: Containing 170 mg of strontium as strontium *L*-lactate.

Medium Dose: Containing 340 mg of strontium as strontium *L*-lactate.

High Dose: Containing 680 mg of strontium as strontium *L*-lactate.