AN AGREEMENT TO PARTICIPATE IN A RESEARCH STUDY

INFORMED CONSENT

TITLE: A Double-Blinded Randomized Controlled Comparative Effectiveness Research Study of Changes in Bone Mineral Density, Blood Chemistries, Self-Reported Quality of Life and Compliance as a Function of Consuming Micronized Versus Non-micronized Forms of Calcium Carbonate With and Without Bisphosphonates

PROTOCOL NO:	Solutions IRB Protocol # 1304180
SPONSOR:	Naturalendo Tech, E-201, Pangyo Innovalley, 622, Sampyung-dong, Sungnam-shi, Kyunggi-do, 463-400, South Korea, 463-400
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STUDY-RELATED PHONE NUMBER(S):	Gilbert R. Kaats, Ph.D. Patti Keith (Study Coordinator) 210-824-4200, 210-601-8080 (24 hours)
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Purpose: This study will compare **c**hanges in bone mineral density, blood chemistries, self-reported quality of life and compliance using a 4-group CER study design comprised of males and females over the age of 21 in which 160 subjects will be divided into 4 study groups.

Methods: Two of the four groups will consist of a total of 80 subjects who are CURRENTLY TAKING BISPHOSPHONATES UNDER THE DIRECTION OF A PHYSCIAN. These 80 subjects will be randomly divided into 2 groups of 40 each. You will be required to discontinue the current calcium supplement you are taking, if any, but to continue taking your bisphosphonates as prescribed. If you are assigned to Group 1, you will add micronized calcium carbonate and vitamin D_3 to your daily dose of bisphosphonates. If you are assigned to Group 2, you will add non-micronized calcium carbonate and vitamin D_3 to your daily dose. Regardless which group you are in, you will take 2 capsules twice each day for a total of 4 capsules per day and will be asked to take the capsules 30 minutes prior to, or with a meal. If you forget to take the morning or noon dose, take all four capsules at the same time with the evening dose.

The other two groups will consist of 80 subjects who will be administered a DXA test in order to be identified as having below average bone mineral density (BMD.) These 80 subjects will be randomly divided into two study groups of 40 each. You will be required to discontinue any calcium supplementation you may currently be taking. If you are assigned to Group 3, you will take micronized calcium carbonate and vitamin D_3. If you are assigned to Group 4, you will take non-micronized calcium carbonate and vitamin D_3. Regardless of which group you are in, you will take 2 capsules twice each day for a total of 4 capsules per day and will be asked to take the capsules 30 minutes prior to, or with a meal. If you forget to take the morning or noon dose, take all four capsules at the same time with the evening dose.

Group 1: Subjects currently taking bisphosphonates (Fosamax®, Actonel®, & Boniva®) with the MCC/D_3
Group 2: Subjects currently taking bisphosphonates (Fosamax®, Actonel®, & Boniva®)with a NMCC/D_3 supplement
Group 3: the MCC/D_3 supplement
Group 4: a NMCC/D_3 supplement

Background on Supplements you will be taking. Compliance with taking calcium supplements has traditionally been very poor. In addition to not being able to observe any noticeable effects of taking calcium, a number of adverse effects have been reported when taking calcium carbonate, the most frequently used calcium supplement derived from limestone. Even among those people who complied with the dosing regimens, the overwhelming majority of research suggests that while calcium carbonate appears to slow down the age-related decline of bone mineral density (BMD), no studies have

been reported suggesting calcium carbonate can reverse these age-related declines in BMD. One contributing factor to the limits of calcium carbonate's effects on bone, may be the body's inability to absorb all the calcium one is taking. In addressing this issue, the sponsor of this research developed a patented technology to micronize the calcium particles making them smaller and more absorbable or bio-available. In addition to its tiny size was thought to increase its absorption, the belief was that the intense activation of zinc via the patented ebonite charging process that could maximize the bioavailability of this calcium.

Pilot studies. In an initial study using ovariectomized rats [60], MCC was found to significantly improve BMD in these animals. Encouraged by these animal results, a pilot study with human subjects was conducted using a double blinded comparison effectiveness research (CER) protocol. A total of 49 participants were randomly assigned to one of four treatment group in which they consumed:

- Group 1: the MCC/D3 supplement (N=15);
- Group 2: a NMCC/D3 supplement (N=15);
- Group 3: bisphosphonate (Fosamax®, Actonel®, & Boniva®) with MCC/D3 (N=10);
- Group 4: bisphosphonate (Fosamax®, Actonel®, & Boniva®) and NMCC/ D3 (N=9)

All participants completed measurements of Dual Energy X-ray Absorptiometry (DXA) of bone mineral density (BMD) at baseline and at 6 months after baseline. Combining bisphosphonate and non-bisphosphonate sub-groups, Table 1 shows comparisons between the treatment groups (Groups 1 & 3) taking MCC/D3 and those taking NMCC/D3 (Groups 2 and 4) ($p=0.009$). Participants consuming MCC/D3 without bisphosphonates increased their BMD by 2%, (4% annualized) while participants taking MCC/D3 with bisphosphonates increased their BMD by 2.3% (4.6% annualized). Data from this study suggest that MCC/D3 can facilitate significant increases in BMD with or without accompanying bisphosphonates.

Requirements: If you choose to enroll in the study, you agree to:

- □ Complete a DXA bone density test at the beginning and end of the 26 week study period. A description of this test is available at www.hmrcenter.com.
- □ Have your blood drawn at the beginning and the end of the study.
- □ Complete the Quality of Life Inventory (QOL) at the beginning and end of the study. A description of this questionnaire is available at www.hmrcenter.com.
- □ Log in weekly to www.hmrcenter.com with your user name and password to record your product usage and adverse effects.
- □ Complete the end of study critique.
- □ Adhere to the procedures for taking the supplements as described above in "Methods". NOTE: IF YOU ARE CURRENTLY TAKING THYROID MEDICATION, YOU MUST TAKE YOUR DAILY DOSE OF THYROID MEDICATION IN THE MORNING AND THE SUPPLEMENT YOU WILL BE ADMINISTERED IN THIS STUDY IN THE AFTERNOON AND EVENING. ADDITIONALLY, IF YOU ARE CURRENTLY TAKING CALCIUM SUPPLEMENTATION IN ADDITION TO BISPHOSPHONATES PRESCRIBED BY YOUR PERSONAL PHYSICIAN, YOU MUST DISCONTINUE USE OF THESE CALCIUM SUPPLEMENTS FOR THE DURATION OF THE 6 MONTH STUDY PERIOD. PLEASE REVIEW THESE PROCEDURES WITH YOUR PERSONAL PHYSICIAN.
- □ Adhere to the procedures for checking in physically at the research center at the end of each 4 week period.

Benefits:

- □ There is substantial evidence to suggest that the program in which you will be participating can improve your bone health with no evidence of adverse effects, and provide other health benefits;
- □ two (2) bone density/body/composition tests--a total value of ~$400;
- □ two (2) comprehensive blood tests-a total value of ~ $880
- □ you will receive a written tracking form to make daily entries of your product usage and on-line access to a site where you will record your weekly data.
- □ you will be entitled to participate in future studies, some of which may begin immediately upon completion of this study.
- □ your participation will provide important scientific information that could help people of all ages and genders to improve their body composition.

Participant Eligibility

In order to participate, you must:

- be an adult over 21 years of age;
- agree to follow the requirements of the study as set forth in this Informed Consent;
- agree to withdraw from the study if becoming pregnant during the study.

You cannot participate if you:

- have conditions that inhibit gastrointestinal absorption of supplements
- are pregnant or nursing;
- have a history of hepatic or renal and cardiac failure
- have a history of osteomalacia or Paget's disease of the bone
- have a history of any other major systemic illness
- are a woman who has received corticosteroids preceding 4-6 weeks
- are allergic or have a sensitivity to study supplement ingredients
- are an individuals who is cognitively impaired and/or who is unable to give informed consent
- have any other condition which your healthcare provider believes may adversely affect your ability to complete the study, its measures, or which may pose significant risk

_____I certify that I meet the above participation criteria (Please initial)

Study Procedures

A Checklist for Participation - Please initial each item 1-17. If you choose to participate:

1. _____Read this Informed Consent, the additional information on the website, and call the research center in order to ask whatever questions necessary to ensure that you understand what will be expected of you.
2. _____Review the form with your physician to ensure that you have no medical conditions that would prevent your participation.
3. _____Call the research center and schedule a time to come in and discuss these requirements with the research coordinator and sign the Informed Consent.
4. _____Schedule your baseline testing that will include:
    - Demographic data (including height)
    - Quality of Life Questionnaire
    - DXA bone density test plus scale weight
    - Blood chemistry test
5. _____Fast for at least 10 hours and complete the blood test at a Quest Diagnostics laboratory location of your choosing
6. _____Although additional information on these tests can be provided upon request, you will not receive results of your baseline tests until the study is complete.
7. _____Adhere to the procedures for taking the supplements. (See "Methods" on page 1of this Informed Consent.)
8. _____You will be given a tracking/reporting form in which you will record your daily product usage. This form must be brought to the research center after completing each 4-wk period along with the bottle of remaining (or empty) product.
9. _____You will also be instructed on the use of the tracking site and procedures for tracking/recording your information weekly on line.
10. _____ By Wednesday after the end of each week, you will log on to hmrcenter.com with your user name and password and record the total number of capsules you consumed in the morning and afternoon/evening during the previous week. You will also rate 14 conditions indicating the extent to which each was a problem during the past week using the following scale: 1=NOT a problem, 2=A MINOR problem and 3=a MAJOR problem. These 14 conditions are as follows: 1) Heartburn, 2) Nausea, 3) Belching, 4) Bloating, 5) Stomach pain, 6) Metallic taste, 7) Excess Gas, 8) Constipation, 9) Vomiting, 10) Pain in arms, legs, joints, 11) Decreased appetite, 12) Dry mouth or increased thirst, 13) Increased urination, 14) Change in heart rhythm.
11. _____ In order to earn the tracking/reporting fee as indicated below under "Payments for Reporting Data and Testing" you must log in on or before midnight (by 11:59 pm) on Wednesday of each week AND you must keep track of your daily product usage AND turn in your written daily tracking log at the end of each 4/week period. There will be NO EXCEPTIONS to this requirement UNLESS you call in to the research center after regular office hours and leave a voice message reporting all of your data. Additionally, if you have a situation where you will not have internet access for a few days, you will need to notify the Research Coordinator AHEAD OF TIME so that a note to that effect can be made on your record. In both of these cases, your data will be counted timely.

12. _____This fee will be paid regardless of product actually consumed as long as you report as such, ie, zero's on days where no product was taken. (The ending testing requirements must also be met in order for you to receive the tracking fees.) Remember, fees are paid for RECORDING, not for taking the product, in order to encourage more candid reporting. IF YOU FAIL TO TAKE THE PRODUCT ON ANY PARTICULAR DAY, YOU WILL STILL LOG IN AND REPORT ZEROS FOR PRODUCT TAKEN, fill out the rest of the form AND YOU WILL BE PAID FOR THAT DAY. Even if, at any time during the study, you decide to stop taking the product altogether, if you continue to report your data (zero product taken) in a timely manner, (and complete the ending tests) you will be paid your tracking fees.
13. _____ You will be issued an 8-week supply (2 bottles labeled Weeks 1-4 and Weeks 5-8) of the product upon completion of baseline testing and entrance interview. You will receive another 4-wk supply (Weeks 9-12) when you check in to the research center after the 28th day of the study. You will discontinue taking capsules out of the first bottle once you complete 4 weeks (day 28). On the first day of the 5th week of the study (day 29) begin using capsules out of the bottle labeled Weeks 5-8.This procedure will be repeated approximately every 28 days of the study period.
14. _____ During each of the check-ins, you will be asked to:
    - turn in your bottle with any unused capsules;
    - discuss with the research coordinator any concerns or negative effects you may have experienced thus far from taking the product.
15. _____Toward the end of the last month of the study, call the Research Center and schedule your DXA TEST. THIS TEST, AS WELL AS THE BLOOD TEST, MUST BE COMPLETED IN A TIMELY MANNER (WITHIN SEVEN DAYS AFTER THE LAST DAY OF THE STUDY PERIOD) IN ORDER TO RECEIVE YOUR REPORTING FEES.
16. _____Upon completion of your ending tests, you will be asked to complete a study critique.
17. _____You will be contacted within 30 days of the end of the study to obtain your test results and payment of your tracking fees.

Payments for Reporting Data and Testing: You will be paid $28.00 for each 4-wk period of the study (a maximum amount of $182.00) that you report your required information in a timely manner as specified above in #11. Your eligibility for the reporting and incentive fees is contingent upon your completion all beginning and ending tests and questionnaires in a timely manner. (See number 15 above.)

It is important to realize that while we strongly encourage you to follow the plan as designed, the recording fees are paid for REPORTING your data, irrespective of how well or poorly you followed the protocol as prescribed. You will receive the reporting fee even if you failed to take the product for that day or if you took less than the specified amount. THE SUCCESS OF THIS STUDY IS ENTIRELY DEPENDENT UPON YOUR TRUTHFUL REPORTING, SO PLEASE BE CANDID ABOUT HOW WELL OR POORLY YOU FOLLOWED THE PLAN AS DESIGNED.

Participant Time Involved: The total time required for the study is approximately 15 hours over the 26 week study period. This time includes completion of the HIPAA Form, the Informed Consent Form, the initial meetings with the Research Coordinator, all of the required tests, completion of all required questionnaires, daily tracking forms, weekly on-line tracking, monthly check-ins, and the final study critique, including travel and wait times.

Potential Risks to Participants: Some potential risks related to your involvement in this study include the following: Log on to www.hmrcenter.com for more information on DXA Bone Density Scan.

□ **Risk to Adults:** It is helpful to understand the level of risk associated with a DXA bone density scan (see below) by comparison with the natural background radiation exposure, which comes from within the body itself (natural occurring radioisotopes....and from terrestrial sources [soil, rocks, building materials, radon], and from extraterrestrial sources [cosmic **rays]). The average annual background radiation exposure associated with a DXA scan is generally less than 1 day of natural background radiation exposure.**

□ **Allergic or other symptomatic reaction to product:** You should consult with your medical care provider prior to your involvement in the study. If you experience any allergic reactions or other adverse effects at any time during this study, you should discontinue product use, notify the researchers, and contact your medical care provider. Clearance from your medical care provider will be required before you will be permitted to continue in the study.

□ **Unknown effects:** Although there are no known adverse effects from the supplement, testing or participation in this study other than those listed above, your personal medical history may present contraindications for your

participation in a research study. Therefore, you are asked to review your participation with your personal physician to insure there are no medical conditions that would prevent your participation. The researchers will try to prevent any problem that could arise because of this research. You should let the researchers know at once if there is a problem and they will help you. However, the Health and Medical Research Center does not provide medical services or financial assistance for injuries or other medical conditions that might occur.

New Findings: During the study, you may be provided with any important new findings about the study supplements. You may use this information in your decision to continue in the study.

Alternatives to Participation: This study is being done for research purposes only and your participation is voluntary.

In Case of Research Related Injury: Integrative Health Technologies, Inc. or Naturalendo Tech does not plan to provide medical services or financial assistance for injuries or other medical conditions that might occur because you are taking part in this research.

Legal Rights: You do not waive any of your legal rights by signing this document.

Confidentiality: Information from this study will be given to the sponsor. "Sponsor" includes any persons or companies which are contracted by the sponsor to have access to the research information during and after the study.
Medical records which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by:

- the sponsor;
- an agent for the sponsor;
- an agent for the study doctor;
- and may be looked at and/or copied for research or regulatory purposes by the Solutions, Institutional Review Board.

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. The results of this research study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations.

Whom to Contact: Contact Patti Keith at 210-824-4200 or 210-601-8080 (24 hours) for any of the following reasons:

- if you have any questions about your participation in this study,
- if at any time you feel you have had a research-related injury or a reaction to the study supplement, or
- if you have questions, concerns or complaints about the research

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:
Solutions IRB is an NIH approved board of medical and lay people who will conduct an independent review of this research to ensure the risks to which you will be exposed and the benefits you receive are explicitly stated and are not excessive. They will not be able to answer some study-specific questions, such as questions about appointment times. However, you may reach them at reviews@solutionsirb.com or call 1-855-226-4472 if you are unable to reach the research staff or if you wish to talk to someone other than the research staff.

Voluntary Participation: Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled. If you have any questions about the research study, tests, supplements, your rights as a participant, or if you wish to withdraw from the study, contact Dr. Kaats or the Research Coordinator at (210) 824-4200. Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any of the following reasons:

- if it is in your best interest;
- you do not consent to continue in the study after being told of changes in the research that may affect you;
- or for any other reason.

You will be given a copy or the original of this dated and signed Informed Consent form.

TITLE: A Double-Blinded Randomized Controlled Comparative Effectiveness Research Study of Changes in Bone Mineral Density, Blood Chemistries, Self-Reported Quality of Life and Compliance as a Function of Consuming Micronized Versus Non-micronized Forms of Calcium Carbonate With and Without Bisphosphonates

Consent Discussion. I confirm that the research study was thoroughly explained to the subject. I reviewed the consent form with the subject and answered the subject's questions. The subject appeared to have understood the information and was able to answer the following questions correctly:

1. What is the purpose of this study?
2. If you decide to be in the study, what will you be asked to do?
3. What is the possible benefit of participating in this study?
4. What are the possible risks of participating in this study?
5. If you decide not to participate in this study, what options do you have?
6. Will participating in this study cost you anything? If so, what will you have to pay for?
7. Do you have to be in this study?
8. If you decide to be in the study, can you leave the study when you want to?
9. What do you need to do in order to be paid the tracking/reporting fees?
10. What options do you have if you decide not to continue in the study? Will you still be paid?

_____ _____ Research Coordinator
Printed Name of Person Conducting _____ Research Assistant
the Informed Consent (IC) Discussion

_____ _____
Signature of Person Conducting the IC Discussion Date

Consent: I have read the information in this consent form. All my questions about the study and my participation in it have been answered. I freely consent to be in this research study. None of my medical records are being requested for this study.

THE NOTICE OF PRIVACY PRACTICES TELLS YOU HOW INTEGRATIVE HEALTH TECHNOLOGIES USES AND DISCLOSES INFORMATION ABOUT YOU. WE ARE REQUIRED TO GIVE YOU A NOTICE OF OUR PRIVACY PRACTICES FOR THE INFORMATION WE COLLECT AND KEEP ABOUT YOU.
I, _____, HAVE BEEN GIVEN A COPY OF INTEGRATIVE HEALTH TECHNOLOGIES, INC.'S NOTICE OF PRIVACY PRACTICES (HIPAA)

_____ _____
INDIVIDUAL'S SIGNATURE **DATE**

You will be assigned a user name. Please select a password for on-line access for reporting our data.

User Name:_____ Password: _____

_____ _____
Printed Name of Participant (First, **Middle Initial,** Last) Date of Birth

_____ _____
Mailing Address Primary E-mail Address

_____ **Note:** Your cell phone will be called first. Please indicate if you prefer not to be contacted here. _____ _____
Cell Phone Home Phone Work Phone

_____ _____ _____
Signature of Participant Date

FOR OFFICE USE ONLY

Study No: 64 Subject ID:_____ Study Subject ID:_____ Protocol #1304180 Bisphosphonates? Yes No

Baseline Wt_____ Ht_____ Table_____ Scan Mode____ Steps_____ BP_____ HR_____ Demog's____ SF ____ Reg'd ____