Official Title: *LCI-BRE-VITD-001*: A Randomized, Open-label Study of High-Dose Vitamin D Versus Standard of Care Vitamin D Supplementation to Evaluate the Impact on Bone Health in Young Women With Early Stage Breast Cancer

NCT# 05016310

IRB-Approved Date: *05/29/2023*

ATRIUM HEALTH
CONSENT TO PARTICIPATE IN A RESEARCH STUDY
AND AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

Sponsor / Study Title: **A Randomized, Open-label Study of High-Dose Vitamin D versus Standard of Care Vitamin D Supplementation to Evaluate the Impact on Bone Health in Young Women with Early Stage Breast Cancer**

Protocol Number: **LCI-BRE-VITD-001**

Principal Investigator: (Study Doctor) **Arielle Heeke, MD**

Telephone: [redacted]

Address: **Levine Cancer Institute** [redacted]

Please read this form carefully. Take time to ask the study doctor or study staff as many questions about the study as you would like. The study doctor or study staff can explain words or information that you do not understand. Reading this form and talking to the study doctor or study staff may help you decide whether to take part or not. You will discuss the Informed Consent Form with the study staff and the study investigator in person, during a telephone call or via a secure video conference call.

If you decide to take part in this study, you must sign and date your name at the end of this form. You cannot take part in this research study until you sign and date this form.
If you agree to take part in the study, you will sign and date the informed consent form either by signing and dating a copy of the printed paper form or by signing and dating electronically using the Florence eConsent platform. Written consent can be done in person or remotely using electronic consent.

After you have signed and dated this paper or electronic Informed Consent Form, you will be given a paper copy or be able to save a copy for your records and/or email a copy to yourself.

This form is for use in a research study that may involve subjects who may or may not have the capacity to consent to take part in the study. Accordingly, when the subject cannot legally consent to take part, pronouns "you" and "your" should be read as referring to the subject rather than the person (legally authorized representative) who is signing this form for the subject.

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INTRODUCTION

The study doctor listed on the first page of this form is asking you to participate in this research study of high dose of vitamin D at Levine Cancer Institute (LCI) and Atrium Health (AH). You are being asked to take part because you have a newly found early-stage breast cancer that has NOT spread to other areas of your body. Your study doctor plans to treat you with systemic therapy (any type of cancer treatment that targets the entire body), including medicine to block or remove hormones (endocrine therapy) or medicine to attack cancer cells in your body (chemotherapy). These treatments in combination with a low vitamin D level can stop the bones from growing and make your bones weak over time, which is a condition called osteoporosis. Osteoporosis may lead to an increased risk for broken bones, resulting in a loss of function, lower quality of life, and greater chance of death. The purpose of this study is to learn whether a high dose of vitamin D can decrease your chance of osteoporosis during anti-cancer therapy and/or arthralgias (joint pain) during endocrine therapy. Researchers will compare high dose vitamin D to the current standard dose by evaluating the effects of vitamin D dose (standard vs. high dose) on bone health and joint pain.

This is a randomized, open-label study. This means you will be randomized (assigned by chance) to one of two "arms" or groups of subjects. One group will be assigned the Experimental arm and receive high dose vitamin D; the other group will be assigned the Standard of Care arm and will take the standard dose of vitamin D. The randomization will be 1:1, which means there is a 50% chance of getting assigned to either arm. The assignment is chosen randomly by a computer system, and all subjects will know which arm they are assigned to.

Whether or not you decide to participate in this study, you will receive treatment for your breast cancer.

You will be one of about 128 women with newly diagnosed breast cancer being asked to participate in this study.

The study will be open for approximately 3 years and your participation will last about 20 months. Taking part in this study is entirely voluntary.

HOW THE STUDY WORKS

You will be asked to participate in the study during your oncology consultation prior to your starting systemic therapy. To participate in this study, you will need to review, sign and date this consent form and provide authorization for the release of your medical records for research purposes. By doing so, you are permitting us to determine if you are eligible (can take part) for this study.

Before you begin the study, the following assessments will be done within 6 weeks prior to your enrollment date (randomization). If some of the assessments were done previously, they may not need to be repeated.

Baseline Procedures:

- Medical history

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- Study-associated medical visit, performed as part of the subject's regular cancer care/follow-up (in medical or surgical oncology clinic or virtually)
- Collection of height and weight
- Eastern Cooperative Oncology Group (ECOG) performance status- measures how well you are able to perform daily living activities
- Blood work to check your vitamin D, calcium, albumin and ovarian function levels
- DEXA scan- a type of X-ray that measures your bone mineral density and bone loss
- Patient-Reported Arthralgia Inventory (PRAI) and overall pain control question- survey filled out by you to measure your joint pain (only if you are receiving endocrine therapy)
- Buccal (cheek) swab collection to learn how different genes can be associated with vitamin D levels (may be collected at baseline or anytime during your participation in the study)
- Baseline symptoms/toxicities
- Medication history

Once you are determined eligible for the trial and agree to participate, you will be randomized to receive either the standard dose or a high dose of vitamin D by mouth for up to 18 months.
Please note: If you are currently taking Vitamin D, you must agree to discontinue the Vitamin D prior to enrollment on the study. A study staff member will call you prior to your enrollment to confirm your discontinuation of the pre-study Vitamin D.
If you are currently taking calcium supplementation, please see Appendix A at the end of this consent form for a preferred list of over the counter calcium supplements. The calcium dose should be at least 500 mg.

<u>Standard of care dose Vitamin D:</u>
You will either receive one of the following 3 dosing schedules, based on your Vitamin D blood level:
1) 50,000 IU Vitamin D2 weekly for 8 weeks followed by 1000 IU daily
2) 1000 IU Vitamin D3 daily or
3) 800 IU Vitamin D3 daily

The schedule may change each time your Vitamin D level is checked.

<u>High dose Vitamin D:</u>
50,000 IU vitamin D2 weekly for 16 weeks, followed by 4,000 IU of vitamin D3 daily.
- If your vitamin D level is **low** after your level is re-checked, you will resume 50,000 IU vitamin D2 weekly for 16 weeks and then 4,000 IU of vitamin D3 daily.
- If your blood vitamin D level is **high**, your vitamin D levels will be checked every 4 weeks and vitamin D dosing will be held until your vitamin D level comes back to normal. Once your vitamin D level is normal, then you will take 4,000 IU of vitamin D3 daily.

Both arms will receive supplemental calcium by mouth daily in addition to the assigned vitamin D study treatment. Please see Appendix A at the end of this consent form for a preferred list of over the counter calcium supplements. A dose of at least 500 mg is strongly preferred. The calcium supplement should not have Vitamin D added to it. You also have the option of receiving a prescription for the calcium supplement; please ask your study doctor if you prefer this option.

ADDITIONAL/MORE DETAILED INFORMATION

A study staff member will call and let you know about the randomization date and study arm you have been "randomized" to (assigned by chance to a study group). Prescription for study Vitamin D will be written by your study doctor and will be filled at your preferred pharmacy. You will take the Vitamin D at home and store at room temperature. Please see section above for information on calcium supplementation.

You should start taking Vitamin D and calcium within 2 weeks of the randomization date. The study staff member will tell by which date you need to begin your study treatment. A study staff member will call you again within 2 weeks to document the date you started study treatment.

During study treatment, the following information will be collected:

As directed by your study doctor; at least every 9 months:

- Clinical assessment information to be collected from your medical or surgical oncology provider during regular visits either in person or using virtual care to include collection of weight and some medications you are currently taking. In the event the you do not have a clinic visit scheduled within 9 months of the previous visit, we will schedule a study-directed visit to see how you are doing.
- ECOG performance status

Every 6 months

- Blood work to check vitamin D and calcium levels

At 12 and at 18 months from Baseline DEXA

- DEXA scan

Every 60 days

Note: *You will be offered to complete the following assessment every 60 days electronically or by paper at home. Paper surveys will be collected approximately every 6 months during your clinic visits. If you opted out from the electronically distributed surveys, you will be notified by a study staff member every 60 days by phone call to complete the following survey on paper for the remainder of study treatment (side effects will be collected by phone call, though).*

- Specific unfavorable effects related and not related to study treatment during study treatment +30 days after it is completed.
- PRAI survey filled out by you to measure your joint pain (only if you are receiving endocrine therapy). One additional survey will be collected if you stop your hormone therapy.
- You will document how much of your study treatment that you take every month.

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YOUR ROLE IN THE STUDY

Taking part in a research study can be an inconvenience to your daily life. Please consider the study time commitments and responsibilities as a research subject when you are deciding to take part. Your responsibilities as a study subject include the following:

- Tell the truth about your medical history and current conditions.
- Tell the study doctor if you have been in a research study in the last 30 days or are in another research study now.
- Tell the study doctor about any problems you have during the study.
- Take the study drug as directed by the study doctor and study staff.
- Do not share the study drug with anyone else. Keep the study drug out of the reach of children and persons of limited capacity to read or understand.
- The study doctor or study staff will talk to you about any food or medicines that you should not take while in this study.
- Use care when driving or using machinery while you are taking the study drug.
- Accurately fill out your study questionnaires.

RISKS OF THE STUDY

Vitamin D

The most common risks of a high dose of vitamin D are:

- Headaches
- Irritability
- Muscle spasms (spasticity)
- Nausea
- Vomiting
- Calcium blood level elevation (hypercalcemia; associated with possible altered mental status, weakness, and/or kidney damage)

Blood Draw Risks

Taking blood from a vein in your body may cause some pain, redness, or bruising and/or infection at the site where the blood is drawn. You may also feel faint or lightheaded. Although rare, an infection at the site of the blood draw is possible.

Allergic Reaction Risks

There is a potential risk of allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions are:

- Rash
- Wheezing and difficulty breathing
- Dizziness and fainting
- Swelling around the mouth, throat, or eyes
- A fast pulse
- Sweating

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Please seek treatment immediately and tell the study doctor and study staff if you have any of these symptoms, or any other side effects, during the study.

DEXA Scan Risks
During the DEXA scan, you will be exposed to radiation. However, your exposure will be lower than with a chest x-ray. The DEXA scans are considered, in general, less harmful than a standard x-ray.

Unknown Risks
You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the study doctor or study staff right away if you have any problems.

ALTERNATIVES TO BEING IN THE STUDY

You do not need to take part in this research study. You may choose not to participate in this study and receive routine care as recommended by your study doctor.

NEW FINDINGS

Any new important information that is discovered during the study and which may influence your willingness to continue participation in the study will be provided to you.

POTENTIAL BENEFITS OF BEING IN THE STUDY

You may or may not receive any benefit from being in the study. The possible benefit of participating in the trial is that you may have a lower rate of bone loss during your anti-cancer treatment and/or joint pain if receiving endocrine therapy. If you take part in this study, other people with your disease may be helped.

COSTS OF BEING IN THE STUDY

The following procedures will be covered by the study: DEXA scans, ovarian labs (estradiol, FSH), albumin level and buccal swab collection.

Your clinic visits, labs other than the ovarian labs collected for this study, and prescriptions will be billed to your insurance in the usual manner.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

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You will not receive payment for taking part in this study.

Your insurance company may not pay for study treatments. You may wish to discuss coverage with your insurance company before agreeing to participate in this research study.

YOUR PAYMENT FOR BEING IN THE STUDY

You will not be paid for being in this study.

COMPENSATION FOR INJURY

In the event that you are harmed as a result of your participation in this study, we will provide or arrange for treatment as necessary. This treatment, as well as other medical expenses, will be billed to you or your insurance company in the usual manner. You do not waive any legal rights by signing this consent form.

If you become ill or are hurt while you are in the study, get the medical care that you need right away.

In no way does signing this consent form waive your legal rights nor does it relieve the investigators, Sponsor or involved institutions from their legal and professional responsibilities.

CONFIDENTIALITY

The records of this study will be kept private. If any report about this research is published, we will not include any information that will make it possible to identify you. However, there is some risk that de-identified data might be re-identified. Also, your record for this study may be reviewed and/or photocopied by the Sponsor, by Atrium Health, or by representatives of the Food and Drug Administration or other government agencies.

To ensure that your information collected for this study will be kept private, your name will not be used whenever possible. A code will be used instead of your name. All of your study data will be kept in a secure location.

This study involves the collection of your private information and biospecimens. Your cheek swab specimen will contain information specific to you such as your name or date of birth and will not be confidential. This specimen and the information gained will not be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject.

Your biospecimens will not be used for profit.

EMAIL COMMUNICATION. By providing my email address, I give permission for Atrium Health and its representative (including third-party agents if applicable) to send me information, reminders, and messages using this means of communication. I authorize Atrium Health to send me

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unencrypted messages using this means of communication, and I understand and accept the risks associated with doing so. Email is not to be used for emergency situations.

AUTHORIZATION TO USE AND DISCLOSE YOUR PROTECTED HEALTH INFORMATION

If you wish to participate in this research study, you

_____

Printed Name of Research Subject

must sign this Authorization. By signing this Authorization, you give all healthcare providers, including Atrium Health, permission to use or disclose (release) your protected health information, both past and present, for the research study described here:

LCI-BRE-VITD-001: A Randomized, Open-label Study of High-Dose Vitamin D versus Standard of Care Vitamin D Supplementation to Evaluate the Impact on Bone Health in Young Women with Early Stage Breast Cancer

The protected health information that we may use or disclose (release) for this research may include all information in your medical record, such as results of physical examinations, medical history, lab tests, or certain health information indicating or relating to a particular condition.

The health information listed above may be used by and/or disclosed (released) to:

- Study investigator and research staff
- Study sponsor and/or its associated companies
- Regulatory or other governmental authorities of the United States or other countries based on this study
- Other persons or agents authorized by the study sponsor
- Atrium Health employees
- Other persons or agencies as required by law or allowed by federal regulations
- Data coordinating centers that will receive and process PHI; and/or;
- Advarra Institutional Review Board (Advarra IRB) or Data Safety and Monitoring Boards.

Atrium Health is required by law to protect your protected health information. By signing this Authorization, you authorize Atrium Health to use and/or disclose (release) your protected health information for this research study. Those persons who receive your protected health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your protected health information with others without your permission, if permitted by laws governing them. Your protected health information may then no longer be protected by the Privacy Rule.

Please note that you do not have to sign this Authorization, but if you do not, you may not receive research-related treatment through this study. However, Atrium Health may not condition (withhold or refuse) your other Atrium Health providers treating you on whether you sign this Authorization.

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You may change your mind and withdraw (take back) this Authorization at any time, except to the extent that Atrium Health or the Sponsor has already used or disclosed your protected health information based on this Authorization. To withdraw this Authorization, you must write to the Study Doctor at the address listed on the first page of this form.

No publication or public presentation about the research described above will reveal your identity without another Authorization from you. If all protected health information that does or can identify you is removed, the remaining information will no longer be subject to this Authorization or federal rules (such as the Privacy Rule) and may be used or disclosed for other purposes.

When the research for which the use or disclosure is made involves treatment and is conducted by Atrium Health: To maintain the integrity of this research study, you generally will not have access to your personal health information related to this research until the study is complete.

At the conclusion of the research study and at your request, you generally will have access to your protected health information. Access to your protected health information in a medical record is described in the Notice of Privacy Practices provided to you by Atrium Health.

When conducting research, the data and results may be used or disclosed for further treatment outcomes research or to research a secondary result. This Authorization will remain in effect after the end of the current study, and any future related secondary study unless it is revoked by the you in writing as described above.

_____

Signature of Research Subject or Research Subject's Legally Authorized Representative

_____

Printed name of Research Subject or Research Subject's Legally Authorized Representative

_____

Date

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

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An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact**:**

- By mail:
  Study Subject Adviser
  [redacted]
- or call **toll free**:
- or by **email**:

Please reference the following number when contacting the Study Subject Adviser: Pro00055909.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BEING A STUDY VOLUNTEER AND WITHDRAWING FROM THE STUDY

Your participation in this study is completely voluntary. You should feel under no pressure to be in the study. If you decide not to be in the study, that will not in any way harm your relations with your doctors or with Atrium Health. You are free to stop being in the study if you change your mind after entering it. This would not harm your relations with your doctors or Atrium Health.

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STATEMENT OF CONSENT

I have read this form and its contents were explained to me. I agree to be in this research study for the purposes listed above. All of my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form.

_____ ____/____/____ _____
Signature of Research Subject Date Time

_____
Printed Name of Research Subject

_____ ____/____/____ _____
Signature of Legally Authorized Representative (if applicable) Date Time

_____
Printed Name of Legally Authorized Representative (if applicable)

STATEMENT OF PERSON EXPLAINING CONSENT

I have carefully explained to the subject or the subject's legally authorized representative the nature and purpose of the above study. There has been an opportunity for the subject or the subject's legally authorized representative to ask questions about this research study. I have been available to answer any questions that the subject or the subject's legally authorized representative has about this study.

_____ ____/____/____ _____
Signature of Person Explaining Consent Date Time

_____
Printed Name of Person Explaining Consent

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Appendix A
Preferred List of Over-the-Counter Calcium Supplements

Note: Calcium supplement should not have added Vitamin D

1. Major oyster shell calcium 500mg
2. Nature's Way calcium citrate complex 500mg
3. Nature's Way calcium citrate/carbonate/malate 500mg
4. Nature's Blend oyster shell calcium 500mg
5. Cooper Complete calcium citrate supplement 500mg