Title: Effects of Liothyronine on Energy Expenditure and Cardiovascular Function

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**RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM**

**TITLE: In vivo characterization of the non-genomic effects of T3 on endothelial and cardiovascular function**

**VCU IRB PROTOCOL NUMBER: HM20005777**

**PRINCIPAL INVESTIGATOR: Francesco Celi, MD, MHSc.**

**SPONSOR: Virginia Commonwealth University**

Please ask the study doctor or the study staff to explain any information in this consent document that is not clear to you. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

**VOLUNTARY PARTICIPATION AND WITHDRAWAL**

Your participation in this study is voluntary. You may decide to not participate in this study. Your decision not to take part will involve no penalty or loss of benefits to which you are otherwise entitled. If you do participate, you may freely withdraw from the study at any time. Your decision to with draw will involve no penalty or loss of benefits to which you are otherwise

**PURPOSE OF THE STUDY**

The purpose of this research study is to compare two different drugs used for hypothyroidism, a disease in which the thyroid is unable to produce enough hormones to regulate some of the body functions. This study may help guide the future development of medicines used in hypothyroidism. You are being asked to participate in this study because you may meet the requirements for study participation.

**DESCRIPTION OF THE STUDY**

Hypothyroidism is a common condition that occurs when the thyroid does not produce enough hormones to regulate body functions. Patients with hypothyroidism are usually given tablets that contain replacement thyroid hormones: LT4 or LT3. Levothyroxine (LT4) is an inactive form of the thyroid hormone that must be converted into its active form (T3) in the body. Several studies showed that LT4 might not be sufficient to produce enough T3 in the body. For this reason, the addition of a synthetic form of T3, called liothyronine (LT3), is thought to improve the symptoms of hypothyroidism.

The U. S. Food and Drug Administration (FDA) has approved both drugs, LT4 and LT3, in tablet form for the treatment of hypothyroidism. However, in this study, these drugs will be given in liquid form. This study is designed to compare LT4 and LT3 to each other and to placebo (a look-alike inactive substance). The study will test whether LT3 works differently than LT4 on the cardiovascular system and help us to better understand the effects of these drugs on your heart and on the metabolism of your body.

Thyroid hormone medications (levothyroxine and liothyronine) are used to treat lo thyroid hormone levels, which are caused by surgery or disease of the thyroid gland. In this study, we use thyroid hormone medications to study their effects on the heart and the vascular system. This is defined as "experimental" use of a drug, where there is no immediate expectation to cure or treat a disease. Although the levothyroxine and liothyronine have been used for many years, there is always the possibility that you may develop an unexpected reaction.

Your participation in this study will include one screening visit (to make sure that you qualify for the study) plus three additional visits. During the three visits, we will measure the effects of the drugs on the heart and the metabolism. Approximately 20 individuals will participate in this study.

The screening visit will last approximately 45 minutes, and it can be scheduled in either the morning or afternoon. Each of the study visits will last approximately 5 hours and a half and will be scheduled in the morning.

**PROCEDURES**

If you decide to be in this research study, you will be asked to sign this consent form after you have had all your questions answered.

At your screening visit (Visit 0), your medical, social and medication history will be recorded and a physical exam will be performed. This exam will include measurements of your weight and vital signs (pulse, blood pressure and temperature). Blood samples will be collected for routine lab tests and to determine eligibility. Approximately 1 to 2 tablespoons of blood will be collected. If you are unsure of your pregnancy status, a blood pregnancy test will be performed. If the result of the test is positive, the medical responsible investigator will notify you and you will not qualify to participate in the study. You will also have an electrocardiogram (EKG - tracing of the electrical activity of the heart) performed.

If you qualify for the study, you will be scheduled for visits 1, 2 and 3. During Visits 1, 2 and 3, you will be randomly assigned (like a flip of a coin) to receive LT3, LT4, or placebo. By the end of the study, you will have received all three treatments (one per visit).

Your first visit (Visit 1) will be scheduled at least 24 hours after your screening visit. Prior to Visit 1, you will need to be fasting for at least 8 hours. An abbreviated history and physical examination with recording of height, weight, waist and hip measurements and vital signs (temperature, pulse, respirations and blood pressure) will be performed. A cannula (small plastic tube) will be inserted in the arm to draw blood. EKG electrodes will be placed on your chest/shoulder/leg and a finger-cuff will be placed to record blood pressure and cardiac function. A cardiac ultrasound (echocardiography) will also be done to measure heart function. We will also use a Bio-Impedance Analysis (BIA) as a mean to measure body composition. Specifically, BIA measures the amount of fluid (water) in your body. You will be asked to lie flat on a bed while four electrodes (two on the foot and two on the hand) are applied. A very low-intensity electrical current (so low that you cannot feel it) is run through your body to measure

the amount of fluid (water) in your body. The test will last approximately 5 to 10 minutes. After these measurements, you will be asked to enter in a room and rest in a chair during the rest of the visit. This room is called an indirect calorimeter chamber and will measure how much energy you are consuming. Once in the room, you will be asked to rest for 30 minutes before one of the study drugs (or placebo) will be administered in liquid form. The study drug administered will be randomly chosen (like the flip of a coin) between LT3, LT4 and placebo. Additional blood will be drawn every 60 minutes (for a total of 4 hours) after the study drug has been administered. Once finished, the canula will be removed from your arm, vital signs (Temperature, pulse and blood pressure) will be obtained, you will be asked to leave the room and an additional ultrasound of your heart will be performed.

Visit 2 and visit 3 will repeat the exact same procedures performed in visit 1. However, the treatment administered will change each time to assure, so that by the end of the study you will have received all three treatments (LT3, LT4, and placebo).

| Visit # | 0 (Screening) | 1 | 2 | 3 |
|---|---|---|---|---|
| Physical assessment | X | X | X | X |
| Baseline blood draw | X | X | X | X |
| | | | | |
| Echocardiogram | | X | X | X |
| Electrocardiogram | X | X | X | X |
| Finger cuff blood pressure measurement | | X | X | X |
| Bio-electrical Impedance Analysis | | X | X | X |
| Metabolic chamber measurement | | X | X | X |
| Blood draw while in the metabolic chamber | | X | X | X |
| LT3 or LT4 or Placebo administration | | X | X | X |

Neither you nor the study doctor will know which study drug you are receiving. This is done (blinding) so that a fair evaluation of results may be made. This information is only available to the study doctor if needed in an emergency.

**ALTERNATIVE TREATMENTS OR PROCEDURES**

This is not a treatment study. The procedures performed are for study related purposes only and not intended to diagnose or treat any specific disease. However, some of the procedures performed in this study are also available in the health care environment. Please talk with regular doctor to see if they are ones you need or want. The following test performed for the study that are also available as a part of medical care include routine laboratory test (chemistry and Hematology, pregnancy test), Electrocardiogram -EKG (EKG - tracing of the electrical activity of the heart), and Echocardiogram ECHO used to measure heart function.

**RISKS AND DISCOMFORTS**

LT3 or LT4 are generally well tolerated but, although unlikely, some side effects are possible:

- Tachycardia (rapid heart rate) (up to 2% in chronic use)
- Skipped heart beats (up to 6% in chronic use)
- Myocardial infarction (up to 2% in chronic use)
- Low blood pressure (up to 2% in chronic use)
- Sudden death (up to 2% in chronic use)
- Anxiety
- Heat intolerance
- Weight loss

Note that you will receive a single dose of each of the study drugs, and that the percentages we are reporting refers to patients who generally have concomitant illnesses and are treated every day with these drugs.

Allergic reactions to LT4 and LT3 are possible. Severe allergic reactions can be life threatening.

The effects of LT3 and LT4 in pregnant women might involve a risk to the embryo or fetus. Therefore, pregnant women may not participate in this study. For similar reasons, women who are nursing an infant may not participate in this study. Women who might become pregnant should use a medically accepted form of birth control.

Other risks to participation in this study include the following:

- Pain or bruising during blood draws. In rare cases, blood draws may results in skin/tissue infection. When possible, blood will be drawn from an existing intravenous cannula (tube) or at the same time as regular (standard) clinical blood draws to minimize the use of extra blood draws.
- The placement of intravenous needles may cause transient pain, and occasional infection or bruising at the insertion site.
- Minor discomfort of your arm or finger during blood pressure measurement.
- Minor discomfort associated with the placement and removal of the electrodes on your skin.

**BENEFITS TO YOU AND OTHERS**

There is no guarantee or expectation that you will receive any medical benefits from being in this study. However, this study will significantly improve the knowledge of the two tested drug to treat hypothyroidism. In addition, information from this research study may lead to a better treatment in the future for people with hypothyroidism.

**USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION**

**Authority to Request Protected Health Information**

The following people and/or groups may request my Protected Health Information:

- Principal Investigator and Research Staff
- Research Collaborators
- Data Safety Monitoring Boards
- Others as Required by Law
- Study Sponsor
- Institutional Review Boards
- Government/Health Agencies

**Authority to Release Protected Health Information**

The VCU Health System (VCUHS) may release the information identified in this authorization from my medical records and provide this information to:

- Health Care Providers at the VCUHS
- Study Sponsor
- Data Coordinators
- Data Safety Monitoring Boards
- Others as Required by Law
- Principal Investigator and Research Staff
- Research Collaborators
- Institutional Review Boards
- Government/Health Agencies

Once your health information has been disclosed to anyone outside of this study, the information may no longer be protected under this authorization.

**Type of Information that may be Released**

The following types of information may be used for the conduct of this research:

| | | |
|---|---|---|
| ☒ Complete health record | ☐ Diagnosis & treatment codes | ☐ Discharge summary |
| ☒ History and physical exam | ☐ Consultation reports | ☐ Progress notes |
| ☒ Laboratory test results | ☐ X-ray reports | ☐ X-ray films / images |
| ☐ Photographs, videotapes | ☐ Complete billing record | ☐ Itemized bill |
| ☐ Information about drug or alcohol abuse | ☐ Information about Hepatitis B or C tests | |
| ☐ Information about psychiatric care | ☐ Information about sexually transmitted diseases | |

**Expiration of This Authorization**

☒ This authorization will expire when the research study is closed, or there is no need to review, analyze and consider the data generated by the research project, whichever is later.

☐ This research study involves the use of a Data or Tissue Repository (bank) and will never expire.

☐ Other (specify):

**Right to Revoke Authorization and Re-disclosure**

You may change your mind and revoke (take back) the right to use your protected health information at any time. Even if you revoke this Authorization, the researchers may still use or disclose health information they have already collected about you for this study. If you revoke this Authorization, you may no longer be allowed to participate in the research study. To revoke this Authorization, you must write to the Principal Investigator.

**COSTS**
The sponsor will provide the study drug. There are no charges for the any of the procedures conducted during the study visits.

**PAYMENT FOR PARTICIPATION**
You will be paid $25 at completion of screening visit (Visit 0), $35 for each completed visit (1, 2 and 3) and $70 as bonus if you complete all scheduled study visits. The maximum total payment is $200. If you withdraw from the study before completion, you will be paid depending on the number of visit you completed.

VCU is required by federal law to collect your social security number. Your social security number will be kept confidential and will only be used to process payment.

**CONFIDENTIALITY**
Potentially identifiable information about you will consist of blood samples and data abstracted from the medical record.

It will be noted in your protected electronic medical record at VCU Health System that you are in this clinical trial. Information about the study including any medications you may receive will be noted in the record. This information is protected just as any of your other medical records are protected.

Your data will be identified by ID numbers, not names, and stored separately from medical records in a locked research area. All personal identifying information will be kept in password-protected files. Access to research data will be limited to study personnel. A data and safety monitoring plan is established.

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 website will include a summary of the results. You can search this Web site at anytime.

Although results of this research may be presented at meetings or in publications, identifiable personal information pertaining to participants will not be disclosed.

In general, we will not give you any individual results from the study. If the study finds any clinically relevant or new findings during the course of the research, the study doctor will notify you. If we find something of medical importance to you we will inform you and your primary care physician with your permission, although we expect that this will be a very rare occurrence.
There are no plans to share any money or profits with you if the use of your sample(s) results in inventions or discoveries that have commercial value.
The information and samples collected as part of this study will not be used or distributed for

future research studies, even if identifiers are removed.

**GENETIC TESTING**

This study will use your samples to sequence all or part of your DNA. Deoxyribonucleic acid (DNA) is the "blueprint" or "recipe" that gives the body's cells instructions on how to do their jobs. Scientists can use a test called whole genome sequencing to determine the order of all or part of the molecules that make up your DNA, like reading all the letters in a book sequencing is usually done to look for changes in the molecules of DNA that may cause health problems.. In this study, genetic testing will be performed by using part of the collected blood during Study visit 1 only. We will study variants in the genes that regulate the response to the thyroid hormone, and genes that regulate the metabolism of thyroid hormone medications to see if any of these changes is associated to a different response to the study medications. These changes are not associated with diseases, and have no clinical importance. We are not planning to screen for genetic diseases, and the information collected are devoid of clinical interest. As such, you will not be informed of the findings of this analysis. We do not expect to develop any commercial product from this study, but please note that the data generated by the use of genetic material in this study are property of the Virginia Commonwealth University. You can decide to decline to participate in the genetic testing but still being part of the non-genetic study. If you decide that you do not want to participate in the DNA part of the study blood for this test will not be collected.

*1.* My blood samples may be stored and used for future research about genetic testing

☐ YES_____ ☐ NO_____
initial initial

**COMPENSATION FOR INJURY or ILLNESS**

If you are injured by, or become ill, from participating in this study, please contact your study doctor immediately. Medical treatment is available at the Virginia Commonwealth University Health System (VCU Health System). Your study doctor will arrange for short-term emergency care at the VCU Health System or for a referral if it is needed.

Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study.

To help avoid research-related injury or illness it is very important to follow all study directions.

**PARTICIPATION WITHDRAWAL**

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent. The reasons might include:

- the study doctor thinks it necessary for your health or safety;
- you have not followed study instructions;
- the sponsor has stopped the study; or
- administrative reasons require your withdrawal.

**QUESTIONS**

If you have any questions, complaints, or concerns about your participation in this research, contact:

**Celi, Francesco, MD, MHSc.**
Virginia Commonwealth University
Sanger Hall 7th Floor – Room 7-007
Richmond, VA, 23298
Phone: (804) 828-9696, (804) 628-1631
Fax: (804) 828-8389

The researcher/study staff named above is the best person(s) to call for questions about your participation in this study. If you have general questions about your rights as a participant in this or any other research, you may contact:

**Office of Research**
Virginia Commonwealth University
800 East Leigh Street, Suite 3000
P.O. Box 980568
Richmond, VA 23298
Telephone: (804) 827-2157

Contact this number to ask general questions, to obtain information or offer input, and to express concerns or complaints about research. You may also call this number if you cannot reach the research team or if you wish to talk to someone else. General information about participation in research studies can also be found at http://www.research.vcu.edu/irb/volunteers.htm.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions. CONSENT

I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered.

By signing this consent form, I have not waived any of the legal rights or benefits, to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this

research study and to contact me in case of abnormalities. I will receive a copy of the consent form once I have agreed to participate.

I give my permission to contact my primary care physician if abnormal results are found.

☐ YES ☐ NO

_____
Participant Name, printed

_____ _____
Participant Signature Date

_____
Name of Person Conducting Informed Consent / Witness
(Printed)

_____ _____
Signature of Person Conducting Informed Consent / Witness Date

_____ _____
Principal Investigator Signature (if different from above) Date