

Effects of epicatechin on patients with statin-induced mitochondrial dysfunction and impaired exercise capacity

Who is conducting the study, why you have been asked to participate, how you were selected, and what is the approximate number of participants in the study?

Dr. Pam Taub, M.D. is conducting a research study to elucidate the effects of a naturally occurring compound (epicatechin) in dark chocolate on your skeletal muscle function. You have been asked to participate in this study because you are between the ages of 30-75, have metabolic syndrome, and have been identified as a non-sedentary individual.

There will be approximately 50 participants at this site; this is the only site participating in the study. The purpose of this study is to see if epicatechin (administered via epicatechin capsules) with simvastatin (a cholesterol lowering medication) will help improve your muscle health after 3 months and prevent decline in muscle function. For this study, you will be either randomized to take epicatechin (the pure compound and not dark chocolate) or take a placebo. A placebo is a tablet that does not contain any epicatechin compound that looks the same as the tablet that does contain the epicatechin. All participants will take simvastatin. During the 3 months of the study, we will ask you not to take any dark chocolate and other products containing flavanols. You will be given a sheet listing foods to avoid and may be asked to keep a food log if you consume foods containing flavanols. Prior to the study, if you are taking any statins, you will be asked to put them on hold for 1-2 weeks during the washout period.

You will have the option to also have a muscle biopsy done. The purpose of the muscle biopsy is to study what happens to your muscle when you take statins and whether taking epicatechin can help decrease some of the side effects that may occur when you take simvastatin.

What will happen to you in this study and which procedures are standard of care and which are experimental?

All of the procedures are experimental and not part of standard of care. All of the visits will take place in the Altman Clinical and Translational Research Institute (ACTRI, 9452 Medical Center Drive, La Jolla, CA 92093). If you agree to be in this study, the following will happen to you: A.

Visit 1: Exercise Test, Fasting blood draw

1. You will be asked to come to the ACTRI in a fasted state.
2. You will be asked to exercise on a stationary bike for about 10-15 minutes. This is part of our screening phase and it will help us determine if you meet the baseline criteria.
3. At this visit, you will also be asked for a blood draw. This is also part of the screening phase and it will help us determine if you meet the baseline criteria. B. Visit 2: Randomization to study drug, Muscle biopsy (optional). The muscle biopsy is an optional part of the study and it is up to you whether or not you wish to participate. 1. For all subjects: If you qualify for the study based on your blood results and exercise test results, you will be asked to return to the clinic for randomization to the study drug.
2. You will be randomly assigned to one of two groups (placebo or epicatechin). This means that there is a 50/50 chance that you will either be taking placebo or

epicatechin (100mg) with the simvastatin (40mg). Epicatechin is present in dark chocolate, and there are no known adverse side effects known with epicatechin.

3. For subjects undergoing optional muscle biopsy: If you choose to participate in the

muscle biopsy, you will be asked to come to the ACTRI in a fasted state. At this visit, Dr. Taub will also be performing a muscle biopsy on one of your thighs. The following is description of the muscle biopsy procedure:

- A biopsy of your leg muscle will be obtained using a special needle. To do a muscle biopsy, an area of skin and the deeper tissues on the outer front portion of either of your lower thighs will be numbed using anesthetic (lidocaine) and a small (1/4 inch) incision made with a scalpel. The numbing medication, (lidocaine) will be given under the skin to minimize the pain. You may feel a stinging sensation the moment the numbing medication is injected under the skin. A very small amount of numbing medication is used so it is very unlikely that you will have any side effects from this medication.
- The special biopsy needle will be inserted through the incision and into your thigh muscle several times and a small amount of tissue will be removed (about the size of a small pea). After the biopsy is completed, deep pressure will be applied to the site for approximately 20 minutes to reduce the risk of bleeding and then a steri-strip tape will be used to close the incision. The risks for the biopsy are explained below. Your muscle will be studied in the laboratory. Some of your muscle may be stored indefinitely and saved for future studies. A total of two biopsies will be performed, one at the beginning of the study and one at the end of the study. Dr. Taub and her team have performed over 100 muscle biopsies with no complications.

C. Between Visit 1 and Visit 4, you will have follow-up telephone calls 1-2 times per month to assess compliance with capsule consumption, possible adverse effects and to review any dietary/lifestyle changes. These phone calls will last approximately 3-5 minutes, and no more than 10 minutes at a time.

1. You **may be** asked to return to the ACTRI for up to 4 visits during your 3 month consumption of placebo or epicatechin, during which we will perform blood tests to assess your levels of epicatechin and other blood tests to assess muscle health. Each visit will last approximately 30 minutes. Not every participant will be asked to return for a blood test.

2. After 3 months, you will return for Visit 4 where the second exercise test, blood draw, and muscle biopsy on your other thigh will be performed.

D. Visit 3: Exercise test, Fasting blood draw

1. You will be asked to come to the ACTRI in a fasted state.
2. You will be asked to exercise on a stationary bike for about 10-15 minutes.
3. At this visit, you will also be asked for a blood draw.

E. Visit 4: Muscle biopsy (optional)

1. You will be asked to come to the ACTRI in a fasted state for your final visit.
2. At this visit, Dr. Taub will perform a muscle biopsy on the other thigh if you have agreed to do so and underwent the first muscle biopsy.

F. Blood and muscle biopsies collected during the study will be stored and investigated. Dr. Taub will have solitary control of the stored specimens, which will be stored for an indefinite period of time, and samples may be analyzed for unforeseen use as funding becomes available. Only authorized research personnel involved in the study will have access to the samples. Your samples will be assigned a unique code to maintain your

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confidentiality. If you wish to withdraw your sample, notify the PI and a member of the research team (contact information is below).

The specimens collected from you and the DNA that they contain may also be used in additional research to be conducted by the University of California personnel collaborating in this research. These specimens, DNA, and their derivatives may have significant therapeutic or commercial value. You consent to such uses. In the future, other investigators from the University of California and its collaborators may study your DNA to

learn more about how genetics affect health. If you decide later that you do not want the specimens collected from you to be used for future research, you may tell this to Dr. Taub, who will use her best efforts to stop any additional studies and destroy the specimens that were collected for this purpose. If as a result of participation in this study we obtain information that could significantly affect your health or well-being, we will attempt to inform you of the existence of this information. You may then decide if you wish to know what we have learned. Your samples will be stored using a de-identified code, which cannot be linked to you by anyone other than research personnel, assuming no security breach. Your samples will be stored in a locked unit which can only be accessed by study personnel, again assuming no security breach. Please note that Federal and State laws generally make it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways: a) Health insurance companies and group health plans may not request your genetic information that we get from this research b) Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums c) Employers with 5 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. Be aware that these laws do not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. G. If at any point you decide to withdraw from the study, we would like to get a final muscle biopsy, blood test, and exercise test at the time of drop-out.

What risks are associated with this study?

Participation in this study may involve some added risks or discomforts. The risks of this study include:

- a) Blood draw:
 - a. pain,
 - b. a bruise at the point where the blood is taken,
 - c. discoloration,
 - d. redness and swelling of the vein,
 - e. infection,
 - f. and a rare risk of fainting.
 - g. At most, 1/8 cup of blood (30mL or 2 tablespoons) will be collected from you at both the initial and final visit. This means a total of up to 1/4 cup (60ml or 4 tablespoons) will be collected from you for the entire study. There is a possibility of a blood test being repeated up to 4 more times over the 3 month study period, which would mean that up to an additional 1/2 cup of blood could be drawn. In that case, the total amount of blood drawn will still be less than 1 cup (200ml or 16 tablespoons), which is less than what is collected at blood donations.

- b) Exercise testing:

- a. arrhythmia,
 - b. low blood pressure,
 - c. chest pain,
 - d. fainting,
 - e. and a rare risk of heart attack.
- c) Consuming Epicatechin
 - a. Allergy
- d) Consuming Statins
 - a. Myositis
 - b. Myalgia

- c. Recurrent muscle pain
- d. Rhabdomyolysis
- e) Optional Muscle biopsy: If you choose to participate in the muscle biopsy, the risks of the muscle biopsy include pain, bleeding, bruising and infection. During the muscle biopsy procedure, you will feel some discomfort like a burning sensation while the anesthetic is being injected. You may also feel some pain in your muscle when the tissue is removed. After the anesthetic wears off, the biopsy site may be mildly tender for 1-3 days. The scar from the muscle biopsy will be about ¼ inch long. There is a very small chance that the scars from the biopsy sites may become thick (hypertrophy). There is also a small chance of bleeding or infection at the biopsy site. If you are concerned about this, you should discuss this with Dr. Taub. These risks will be minimized with pressure and bed rest after the procedure.
- f) Statins on hold: If you are currently taking statins, this 1-2 week period without statins may increase your risk of cardiovascular events, such as heart attack or stroke.
- g) A potential loss of confidentiality. The UCSD Institutional Review Board (IRB), the FDA, and other government agencies may inspect the study records. To minimize the risk of a potential loss of confidentiality, subjects will be assigned a unique subject code and their blood samples will be assigned a different unique specimen code. A separate paper document will link patient identifiers with subject codes and specimen codes. This document will be kept in a secure location in a locked cabinet. Only the PI and study coordinator will have the key to the cabinet. No research documents will have any patient identifiers and will only be labeled with the unique assigned subject codes.

Because this is a research study, there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings. You will be told if any important new information is found during the course of this study that may affect your desire to continue.

What are the alternatives to participating in this study?

This study is optional. You may choose not to participate in this study at any time.

Can you choose to not participate or withdraw from the study without penalty or loss of benefits?

Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without penalty or loss of benefits to which you are entitled. If you decide that you no longer wish to continue in this study, you will be required to call Dr. Pam Taub.

What benefits can be reasonably expected?

There may or may not be a direct benefit to you from these procedures. You may be withdrawn from the study if Dr. Taub believes that it is in your best medical interest. You may also be

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withdrawn from the study if you do not follow the instructions given you by the study personnel. Also, the investigator may learn more about the effects of epicatechin on those who are taking simvastatin.

What if you are injured as a direct result of being in this study?

If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at 858-246-4777 for more information about this and to inquire about your rights as a research subject or to report research-related problems.

Will you be compensated for participating in this study?

For those participants who undergo the muscle biopsy: you will receive up to \$300 for participating in this research. \$150 will be given when you receive the epicatechin capsules initially and \$150

upon the completion of the study.

For those participants who do not undergo the muscle biopsy: you will receive up to \$100 for participating in this research. \$50 will be given when you receive the epicatechin capsules initially and \$50 upon the completion of the study.

For all participants: If at the initial exercise test visit you are taking statins, you will be asked to return to repeat the test after the statin-washout period determined by Dr. Taub. Compensation of \$20 will be provided for this additional visit. You **may be** asked to return to the ACTRI for up to 4 visits during your 3 month consumption of placebo or epicatechin, during which we will perform blood tests to assess your levels of epicatechin and other blood tests to assess muscle health. Each visit will last approximately 30 minutes. For each of these additional blood draw visits, you will be given \$20 (for a total of \$80 for up to 4 visits). Not every participant will be asked to return for additional blood tests.

Are there any costs associated with participating in this study?

There will be no cost to you for participating in this study. We will be providing free parking for all visits related to the study.

What about your confidentiality?

Research records will be kept confidential to the extent allowed by law. Your research records will be labeled with a code number and may also contain certain patient identifiers as well. The list that matches your name with the code number will be kept in a locked file in the PI's locked office. Any research records that identify you will be kept only as paper records in a secure CTRI location, or as files behind the secure UCSD computer firewall. Any presentations or publications from this information will not identify you. Research records may be reviewed by the UCSD Institutional Review Board, the FDA, the Federal Office of Human Research Protections.

Who can you call if you have questions?

Dr. Pam Taub and/or her designee has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Dr. Pam Taub's Research Team below during the day or call 619-290-1252 (pager) after 5:00 PM.

Principal Investigator (UCSD)	Pam Taub, MD	858-246-2497
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Study Coordinator (UCSD)	Taub Research Group General Line Ashley Rosander, BS Aryana Pazargadi, BS	858-246-2510 858-246-2342 858-246-2406
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Dr. Pam Taub (the principal investigator of this study) and her colleague, Dr. Francisco Villarreal, are both co-founders and minority shareholders in Epirium Bio (formerly Cardero Therapeutics) (a non-publicly traded company). Epirium Bio is developing drugs related to epicatechin for use in treatment of muscle disorders. This study is not sponsored by Epirium Bio and is fully funded by the American Heart Association. For questions, please contact the research coordinator at 858-246-2510 and you will be connected to the appropriate staff at the Conflict of Interest Committee.

Your signature and consent

You have received a copy of this consent document and a copy of the "Experimental Subject's Bill of Rights" to keep.

For all participants, please check one or more of the boxes below:

- I consent to have my blood samples stored for possible use in future studies at the PI's discretion as outlined above.
- I DO NOT consent to have my blood samples stored for possible use in future studies.
- I DO NOT consent to provide muscle samples for this study and will not

participate in the muscle biopsy.
For those participants who choose to undergo the optional muscle biopsy:

- I agree to provide muscle samples for this study and I consent to have these samples stored for possible use in future studies at the PI's discretion as outlined above.
- I agree to provide muscle samples for this study but DO NOT consent to have these samples stored for possible use in future studies.

Note: You may change your answer at any point during the course of the study by notifying Dr. Taub or the study coordinator.

By signing below, you are agreeing to participate in this study.

Subject's name (print)

Date

Subject's signature

Researcher obtaining consent's name (print)

consent's signature Date

Researcher obtaining