A Single Center Dose Ranging Pilot Study of (+)-Epicatechin in Non-ambulatory Adolescents With Duchenne Muscular Dystrophy and Pre-symptomatic Cardiac Dysfunction

NCT02964377

February 9, 2017

Title of research study:UCD0316: A single center dose ranging pilot study of (+)-epicatechin (Cardero Therapeutics, Inc) in non-ambulatory adolescents with Duchenne muscular dystrophy and pre-symptomatic cardiac dysfunction

Investigator: Craig McDonald, MD and Erik Henricson, PhD, MPH

Why am I being invited to take part in a research study?

We invite your child to take part in a research study because he is a non-ambulatory adolescent with Duchenne muscular dystrophy and pre-symptomatic cardiac dysfunction.

What should I know about a research study?

(Experimental Subject's Bill of Rights)

- Someone will explain this research study to you, including:
  - The nature and purpose of the research study.
  - The procedures to be followed.
  - Any drug or device to be used.
  - Any common or important discomforts and risks.
  - Any benefits you might expect.
  - Other procedures, drugs, or devices that might be helpful, and their risks and benefits compared to this study.
  - Medical treatment, if any, that is available for complications.
- Whether or not you take part is up to you.
- You can choose without force, fraud, deceit, duress, coercion, or undue influence.
- You can choose not to take part.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- You can ask all the questions you want before you decide.
- If you agree to take part, you will be given a signed and dated copy of this document**.**
- If you agree to take part, you will be given a copy of this document.

Who can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team:

Craig McDonald, MD	Study PI	at phone number 916-734-2923
Erik Henricson, P.H.D ,MPH	Co-PI	at phone number 916-734-5294
Candace Aguilar BS	Study Coordinator	at phone number 916-734-0968
Sasa Yang M.S	Project Manager	at phone number 916-734-8898

UC Davis Department of Physical Medicine and Rehabilitation
4860 Y Street, Suite 3850
Sacramento, CA 95817

In addition to the phone number above, there is a 24-hour non-emergency telephone number for the UC Davis Medical Center (UCDMC) Hospital Operator. It is (916)734-2011. If you call the UCDMC Hospital Operator, tell the Operator you are participating in a research study and you wish to talk to the PM&R on call. In the case of an emergency, dial 911 from any phone.

For IRB Use

APPROVED by the Institutional Review Board at the University of California, Davis	
Protocol	APPROVED
951753	February 9, 2017

This research has been reviewed and approved by an Institutional Review Board ("IRB"). Information to help you understand research is on-line at http://www.research.ucdavis.edu/policiescompliance/irb-admin/.You may talk to a IRB staff member at (916) 703-9151, IRBAdmin@ucdmc.ucdavis.edu, or 2921 Stockton Blvd, Suite 1400, Room 1429, Sacramento, CA 95817 for any of the following:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

Why is this research being done?

This research study will test an investigational drug called (+)- Epicatechin. (+)-Epicatechin is purified from tea as a nutritional extract and is also found in cocoa. It has been shown to improve muscle structure and function in previous studies of animals and humans. (+)-Epicatechin will be evaluated for the treatment of non-ambulatory children and teens with Duchenne muscular dystrophy (DMD). The main objective of this study is to evaluate the effect and safety of 3 different doses of epicatechin over a short period of time in 15 people with DMD. The study will also look at changes in biomarkers (small molecules in the blood) that will determine whether the study drug is affecting the function of the heart and skeletal muscles. If the results are positive, researchers will conduct a longer and larger study to evaluate whether the study drug can make people feel better.

This study drug is not currently approved by the Food and Drug Administration (FDA) for the treatment of DMD.

How long will the research last?

We expect that your child will be in this research study for up to 12 weeks for a total of 5 visits. Each visit on average will be expected take about 3 hours.

How many people will be studied?

We expect 15 people will be in this research study at UC Davis.

What happens if I say yes, I want to be in this research?

Study Procedures: The study activities and when they occur are listed in the table below, and occur at 5 different visits (Screening, Baseline, Week 2, Week 4 and Week 8). Detailed information about each activity is included after the table.

Study Procedures Matrix: Open-label dose-ranging study of (+)-epicatechin in non-ambulatory DMD

Assessments	Primary Phase				
	Screening	Baseline	Week 2	Week 4	Week 8
	Day -28 - Day 0		Day 14*	Day 28*	Day 56*
Review of Entry Criteria	X				
Medication Administration		- Daily -			
Blood Tests to Evaluate Pharmacokinetics		X	X	X	X
Blood Tests to Evaluate Drug Activity		X	X	X	X
Blood Tests to Evaluate Drug Safety	X	X	X	X	X
Other Safety Evaluations					
Medical History		X	X	X	X
Physical/Neurological Examination		X	X	X	X
AE/Concomitant Medications		X	X	X	X
Urinalysis		X	X	X	X
12-lead Electrocardiogram		X	X	X	X
Clinical Efficacy Assessments					
Cardiac Function					
Screening Echocardiogram	X				X
Cardiac MRI		X			X
Strength, Range of Motion and Mobility					
Kinect Reachable Surface Area		X		X	X
Performance of the Upper Limb PUL)		X		X	X
6Amin cycle test w/metabolic testing		X		X	X
Person-Reported Outcomes					
POSNA PODCI		X		X	X
PROMAUL		X		X	X
Body Composition / Anthropometrics					
Height, Weight	X	X		X	X
DEXA for Body Composition		X		X	X

*** Visits may occur +/- 2 days**

Informed consent (30 mins) (At Screening)

Before we begin any procedure we will review this consent form with you and answer any questions that you might have. After you sign the consent form we will provide you with a copy.

Review of Entry Criteria (At Screening)

Your study doctor will review the inclusion and exclusion criteria to make sure that it is safe for your child to be in the study.

Study Medication Administration

If your child is enrolled into the study, he will begin taking (+)-epicatechin at the baseline visit.

- Medications will be dispensed for the entire period of time between study visits. The site will dispense study medication to you and you will keep a medication log to document all study medication dispensed. You will be instructed to give the study medication to your child per the dosing schedule, every day during the eight-week treatment period. You will be asked to return your empty medication container and/or any remaining pills at the next visit.

- Your child will swallow pills of (+)-epicatechin with a total daily dose of 50mg/day per day, 75mg/day, or 150mg/day. This is an escalating-dose study. This means that the first 5 participants will receive 50mg per day, the second 5 will receive 75mg per day, and the third 5 will receive 150mg per day. The study medication will be supplied as a clear 25mg gelatin capsule. Your child will take capsules in the morning at approximately 7:30AM at least 15 minutes before the morning meal and again in the evening at approximately 7:30PM at least 1 hour after the evening meal. If you are in the second or third group, your child will also take capsules around lunch time or mid-day.

Blood Testing

We will collect about **15ml (5ml=1tsp)** of blood from a vein in your child's arm at every visit. Details of what the blood will be used for includes the following:

Blood Testing to Evaluate Pharmacokinetics (5ml total): Pharmacokinetics testing means that we will look at how fast the study medication appears in your child's blood stream after taking it by mouth. Your child will have about 2.5ml (about ½ teaspoon) of his blood drawn through a vein in his arm, and then he will take the study medication in the clinic. Two hours later, **he will have a second blood draw**, again of about 2.5ml.

Blood Testing to Evaluate Drug Activity (5ml total): At the same time and using the same needle that your child has blood drawn for the first pharmacokinetics sample, we will collect another 5ml of his blood (about a teaspoon). This will be so that we can do a series of tests of different biomarkers (small chemicals in his blood) that will help us find out whether the drug is having the expected effect on your child's heart and muscles.

Blood Testing to Evaluate Drug Safety (5ml total): At the same time and using the same needle that your child has blood drawn for the first pharmacokinetics sample, we will collect another 5ml of your child's blood (about a teaspoon). This will be so that we can do routine laboratory safety tests to make sure that he has normal liver, kidney and blood/bone marrow functions. This will help us to monitor his safety while he is taking the study drug. Safety tests and the amount of blood they require include:

- Complete blood count and differential (2.5 ml)
- Comprehensive blood chemistry panel (2.5ml)

Other Safety Evaluations

- *Medical history:* We will ask your child questions about medical conditions, and whether they are old or new since he started the study.
- *Physical and Neurological Examination:* The study doctor will do a complete physical and neurological examination.
- *Vital signs:* We will measure your child's weight, height, blood pressure and breathing rate.
- *Adverse events/ Medications:* We will ask you about medications that your child is taking and if anything has happened since the last visit that hurt or was out of the ordinary with regard to his health.
- *Urinalysis:* Your child will provide a urine sample.
- *12-lead Electrocardiogram (ECG):* Your child will have a routine test to look at the electrical activity of your heart. A study assistant will put sticky pads on his chest, and then he will lie still

while the machine records the electrical activity of your heart. It will help us to determine how well his heart is functioning.

Clinical Efficacy Assessments

We will do a series of laboratory tests to look at how well your child's heart functions, how well he is able to do some upper body exercise, and to test his body composition (i.e. how much bone, muscle, and fat is in his body).

Your child will be asked to perform several exercise tests including the following measures:

- *Echocardiogram:* Your child will go to the pediatric cardiology lab, where a technician will take measurements of his heart and how it is beating. The technician will apply some gel to his skin, and will use an ultrasound wand to see and record images of his heart. It will take about 1 hour.
- *Cardiac MRI:* Your child will have a cardiac magnetic resonance (cMRI) scan of his heart to see how well it is beating. You will complete a safety questionnaire to make sure that your child does not have any metal in his body that could react to a strong magnetic field. If he is OK to scan, he will lie very still in the MRI machine, which is a long tube. It will make loud clicking and buzzing noises as it takes pictures. The MRI technician or study coordinator will give your child ear plugs and headphones so that he can listen to music and the technician's instructions. The cMRI will take about 45 minutes.
- *Kinect Reachable Surface Area Test:* Your child will sit in a chair (or his wheelchair) in front of a Microsoft Kinect 3-D camera and he will follow instructions on a large screen. He will be asked to follow an example movie and move his arms over his head and around his body as best as he is able. The Kinect camera will record how much he can move his arms. The test will take about 10 minutes.
- *Performance of the Upper Limb Test:* A research kinesiologist will ask your child to perform a series of everyday tasks that involve your child using muscles in his shoulders (like reaching over his head to stack cans), muscles in his arms and elbows (like using a fork or spoon) and muscles in his hands (like writing or picking up small objects). The test will take about 20 minutes.
- *Assisted Six-Minute Cycle Test with Metabolic Testing:* Your child will sit in a chair at a table, where he will "pedal" an arm cycle machine for 6 minutes. The machine will provide some assistance with the exercise, and will help him to keep time while exercising. The machine will measure how much force he is able to generate while he is exercising. He will wear a breathing mask that will measure how much oxygen that he breathes in, and how much carbon dioxide he breathes out. The test will take about 15 minutes.
- *Person-Reported Outcome Measures:* You will be given two questionnaires (the PODCI and the PROM-UL). Both questionnaires ask you about your child's ability to complete everyday tasks related to his mobility and arm and hand function. The questionnaires may take up to 1 hour to complete. You can choose to do them on your own using a pen and paper, or as an interview with a research assistant.
- *Body Composition by Dual energy X-ray Absorptiometry (DEXA):* Your child will lie still on the bed of the DEXA scanner. The scanning arm will pass over his body one or more times and will

make a computerized X-ray image of his whole body. He will not feel anything during the scan, but he will be asked to lie very still. The DEXA will take about 10 minutes.

What are my responsibilities if I take part in this research?

You will be responsible for telling the doctor if your child has any new or worsening medical symptoms or problems during the time you receive the study medication as part of this study if your child takes part in this research. It is important that you tell the doctor even if symptoms or problems are mild or you do not think they are related to study drug.

You will need to complete a drug diary and bring your medication to each study visit.

Please call if you have any questions about study medication or about the use of other drugs during the time that you receive study medication.

Contact the doctor immediately if an overdose of study drug happens or is suspected.

What happens if I do not want to be in this research?

You may decide not to take part in the research and it will not be held against you as participation is on a voluntary basis.

Instead of being in this research study, your choices may include participating in other available clinical trials or choosing not to participate at all.

What happens if I say yes, but I change my mind later?

Your child can leave the research at any time and it will not be held against you.

If you decide that you want your child to leave the research, you should contact the investigator so that the investigator can recommend proper follow up care and any necessary safety tests.

If your child stops being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from his routine medical care. If you agree, this data will be handled the same as research data.

Is there any way being in this study could be bad for me?

Potential Risks

Risks of Study Medication (Epicatechin)

Hypotension (low blood pressure). Given the reported effects of epicatechin on blood vessels, a potential risk may be associated with hypotension. With cocoa based studies, blood pressure reducing effects are only reported in humans that have high blood pressure. There is the possibility that patients undergoing drug treatment for high blood pressure if given epicatechin may develop hypotension.

Migraines (Headaches). The consumption of cocoa products has been associated with increased likelihood of migraine development. Epicatechin may increase the chances for migraine development in certain individuals.

Bleeding. Anti-clotting like effects have been described in a limited number of reports on the effects of cocoa, although no such reactions have been seen to date. It will be important not to take any “blood thinning” medications (example: Asprin and Advil) during the study without consulting the study doctor.

Other Side Effects: (+)-epicatechin is an experimental study medication that has not been used in people with Duchenne muscular dystrophy. That means that there may be side effects that occur that we do not know about.

Risks of Blood Tests

The risks of blood drawing include soreness or bruising at the site of the needle. A local numbing cream (EMLA) may be applied to the area. There are no side effects associated with the use of this cream. Rarely, a more serious injury, such as hematoma (bleeding under skin) or infection may develop. Repeated blood draw may increase the chance of the risks above.

Risks of Electrocardiogram (ECG)

The ECG has no known risks.

Risks of Echocardiogram

Your child may be asked to hold his breath or hold still for a few seconds in an uncomfortable position while the echocardiogram tech takes pictures of his heart.

Risks of Cardiac Magnetic Resonance Imaging (cMRI)

Some people who are claustrophobic (afraid of enclosed spaces) can feel anxious when having an MRI scan. Your child will be able to talk with the MRI technician while he is in the scanner, and a research assistant can be in the scanning room with him while he has the test. To avoid any dangerous health risks, it is very important to correctly complete the MRI safety screening questionnaire to make sure he does not have any metal in his body that could be affected by a strong magnetic field.

Risks of Strength Testing, Range of Motion and Functional Assessments

At this time, there are no known risks associated with functional evaluation or muscle strength testing methods used in this protocol. However, your child may experience mild muscle soreness the day after muscle testing.

Risks of Person-Reported Outcome Questionnaires

The functional ability questionnaires ask about how easy or hard it is to perform daily tasks, and they can make some people feel frustrated, sad or angry if questions ask about things they cannot do, or things they used to be able to do. Your child does not have to complete any questions that make him feel uncomfortable.

Risks of DEXA Body Composition Scans

This study involves a low radiation exposure that is less than other diagnostic tests using ionizing radiation. The amount of radiation exposure received in this study is below the levels that are thought to result in a significant risk of harmful effects.

Will being in this study help me in any way?

It is possible your child will not experience any direct benefit as a result of his study participation. The research team will use the data to decide whether there is enough evidence to do a longer study that is designed to improve the health of people with DMD. The data collected during this trial may provide information that will benefit the scientific community as well as other individuals with DMD.

What happens to the information collected for the research?

Efforts will be made to limit use or disclosure of your child's personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect your child's information include the IRB and other University of California representatives responsible for the management or oversight of this study.

The IRB and the Food and Drug Administration will be granted direct access to your child's research records to conduct and oversee the study. We may publish the results of this research. However, we will keep your child's name and other identifying information confidential.

During your child's participation in this research, data will be collected about your child. When the de-identified data and any specimens, such as blood or tissue, are taken from him for this study, they will become the property of the University of California. The specimens may be used in this research, may be used in other research, and may be shared with other organizations. The specimens could lead to discoveries or inventions that may be of value to the University of California or to other organizations. Under state law you do not have any right to money or other compensation stemming from products that may be developed from the specimens.

If you agree to share the biological specimen(s) collected from your child, please initial here. _____

_____

Otherwise, your child's specimen will be destroyed at the end of this study. Information regarding biomarkers and outcome of the study will not be shared.

The sponsor, monitors, auditors, the IRB, the Food and Drug Administration will be granted direct access to your child's research records to conduct and oversee the study. We may publish the results of this research. However, we will keep your child's name and other identifying information confidential.

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 your child. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If we access protected health information (e.g., your medical record), you will be asked to sign a separate form to give your permission. Your child's medical records may become part of the research record. If that happens, your child's research records may be looked at by the sponsor of this study and government agencies or other groups associated with the study. They may not copy or take his personal health information from his medical records unless permitted or required by law.

Federal law provides additional protections of your child's medical records and related health information. These are described in the UC Davis Health System Notice of Privacy Practices (http://www.ucdmc.ucdavis.edu/compliance/pdf/notice.pdf) and in an attached document.

Can I be removed from the research without my OK?

The researchers in charge of the study can remove your child from the research study without your approval if new information regarding the safety of (+)- Epicatechin is discovered. We will tell you about any new information that may affect your child's health, welfare, or choice to stay in the research. The researchers can also remove him from the research study without your approval if you do not or cannot follow the study instructions and schedule.

What else do I need to know?

There is no charge for you to participate in this study. Neither you nor your insurance carrier will be charged for your child taking part in the research. All costs associated with the study will be paid by the sponsor/department.

It is important that you promptly tell the person in charge of the research if you believe that you have been injured because of taking part in this study. If he is injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by University or the study sponsor or may be billed to your insurance company just like other medical costs. The University does not normally provide any other form of compensation for injury.
Your child will not be compensated for taking part in this study.

For more information about no compensation, you may call the IRB Administration at (916) 703-9151 or email at IRBAdmin@ucdmc.ucdavis.edu .

Signature Block for Children

Your signature documents your permission for the named child to take part in this research.

Printed name of child

Signature of parent or individual legally authorized to consent to the child's general medical care

Date

- ❑ Parent
- ❑ Individual legally authorized to consent to the child's general medical care (See note below)

Printed name of parent or individual legally authorized to consent to the child's general medical care

Note: Investigators are to ensure that individuals who are not parents can demonstrate their legal authority to consent to the child's general medical care. Contact legal counsel if any questions arise.

Signature of parent

Date

Printed name of parent

If signature of second parent not obtained, indicate why: (select one)

- ❑ The IRB determined that the permission of one parent is sufficient.
- ❑ Second parent is deceased
- ❑ Second parent is unknown
- ❑ Second parent is incompetent
- ❑ Second parent is not reasonably available
- ❑ Only one parent has legal responsibility for the care and custody of the child

Assent

- ❑ Obtained
- ❑ Not obtained because the capability of the child is so limited that the child cannot reasonably be consulted.
- ❑ Waived by the IRB because the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of the research.

For IRB Use

APPROVED by the Institutional Review Board at the University of California, Davis	
Protocol	APPROVED
951753	February 9, 2017

Signature of person obtaining consent and assent	Date

Printed name of person obtaining consent

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