Columbia University Medical Center Consent Form

Attached to Protocol: IRB-AAAC9240
Principal Investigator: Michio Hirano (mh29)
IRB Protocol Title: MELTIMI Study (Idebenone and MELAS)

Consent Number: **CF-AAAF5932**
Participation Duration: 15 weeks
Anticipated Number of Subjects: 21

Contact

Contact	Title	Contact Type	Numbers
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Research Purpose

The purpose of this study is to find out whether a medication called Idebenone has the potential to be beneficial to patients with MELAS and the A3243G mitochondrial DNA mutation, and to determine whether it is safe and well tolerated.

Information on Research

This consent describes a research study and what you may expect if you decide to participate. You are encouraged to read this consent form carefully and to ask the person who presents it any further questions that you may have before making your decision whether to participate. This form has important information and telephone numbers, so you should keep this copy to refer to as the study proceeds.

Mitochondria are sometimes called the powerhouses of the cell because they provide energy. Mitochondria have their own DNA (mtDNA) and mitochondrial diseases are often caused by mutations in the mitochondrial DNA which result in poorly functioning mitochondria. This can cause a variety of symptoms including lack of energy, seizures, strokes and other medical problems.

This will be the first study such as this to be conducted in patients with MELAS. Idebenone is a synthetic molecule that has the capacity to increase the production of cellular energy and has helped patients with Friedreich's Ataxia, a disease associated with mitochondrial problems. This study will attempt to determine if Idebenone improves the magnetic resonance spectroscopy (MRS) results in participants who carry the A3243G mitochondrial mutation and who are at least minimally affected by the mutation. We want to perform a first study of idebenone in patients with MELAS to make sure that it is justified to proceed check to larger and longer trials. Participants will be randomized to one of two different doses of Idebenone, or a placebo (pill that looks like Idebenone, but does not contain

Idebenone) for a period of 1 month. Participants will have various tests performed prior to and again after taking the study medication for 1 month. We will evaluate whether there is any improvement in test outcome while on study medication. Additionally, we will evaluate whether the study medication caused any unwanted side effects. Should idebenone prove to have potential for the treatment of MELAS, the results of this 1 month trial will be used to guide a longer clinical trial.

Should you be taking any other investigational medications, we request that you discontinue these other medications at least prior 1 month to attending a screening visit for this study. Should you be taking CoQ10 you may continue taking it providing the dose is no more than 100mg per day. You may re-start your investigational medications (increase your CoQ10 dose) once you have completed this study. In signing this consent you agree to these stipulations.

You have been selected to participate in this study because you carry the A3243G mitochondrial mutation. Participants will come to Columbia University 2 to 3 times over a period of up to 15 weeks. These visits include: 1) Screening Visit, 2) Baseline Visit, and 3) Outcome Visit. The screening and baseline visit may take place within one trip to NYC, in which case the participant would only travel to NYC twice during the course of the study. Participants will be contacted via telephone approximately two weeks after the Outcome Visit to assess existing and new adverse events. Participants who withdraw early will be contacted approximately 2 weeks after withdraw to assess any existing and new adverse events. Investigational site visits will include cerebral MRS scanning to measure lactate concentration, venous lactate concentration, energy production in blood cells, 6-minute walk test, fatigue and quality of life questionnaires, neurological and physical exams, vital signs, EKG, and safety blood and urine analysis. All visits will occur on an outpatient basis, and participants will stay at a local hotel as needed.

This study will be performed at one site and it will include a total of up to 21 patients between the ages of 8 and 64 years old.

STUDY PROCEDURES

Screening Visit: informed consent, medical history, EKG, physical and neurological exam, blood sampling, urine pregnancy test (for females of childbearing potential), urine sample (safety laboratory tests), medication review. Visit will last approximately 4 hours.

Baseline Visit (to occur within 2 months of screening visit): fatigue and quality of life questionnaires, medical history, blood sampling, electrocardiogram (EKG), urine sample for pregnancy testing (for females of child bearing potential), urine sample (safety laboratory tests), physical and neurological exam, magnetic resonance spectroscopy (MRS), motor function test (6 minute walk), receive patient diary and study medication (Idebenone or placebo). You will be instructed on the use of the patient diary and on how and when to take the study medication. The screening and the baseline visit may occur together, in which case participants would only travel to NYC twice during the course of this study. Visit will last approximately 6-7 hours.

Days 8, 15 and 22 (+/- 2 days) after starting study medication- we will contact the study participant to determine his/her well being and whether he/she has developed any health related issues, and lastly we will ask whether he/she has started taking any new medications since the previous visit or telephone call.

Outcome visit at 1 month: fatigue and quality of life questionnaires, medical history, blood sampling, urine pregnancy test (for females of child bearing potential), urine sample(safety laboratory tests), electrocardiogram (EKG), physical and neurological exam, magnetic resonance spectroscopy (MRS), motor function test (6 minute walk), review patient diary, assess adverse events, and return unused study medication. Visit will last approximately 6-7 hours

Follow-up consult (approximately 2 weeks after outcome visit) or premature withdraw: participants will be contacted by a member of the research team to assess existing and new adverse events.

DESCRIPTION OF PROCEDURES

EKG- a standard hospital EKG will be performed.

Physical and neurological exam- a standard physical and a basic neurological exam will be performed.

Magnetic Resonance Spectroscopy (MRS)-A standard brain MRS will be performed. An MRS is similar to an MRI in that the participant will lie in the MRI machine for the test. The scan will last approximately 45 minutes. Adult participants who require sedation for the MRS will be allowed to take a small dose of valium (5-10mg) prior to scanning.

Blood sampling- blood sampling will be performed according to standard hospital procedures. Approximately 2 tablespoons will be drawn at each visit for basic laboratory chemistry.

Urine sampling-approx. 1/4 cup of urine will be collected at each visit for laboratory analysis.

Motor testing (6 Minute Walk Test)- participants will be requested to walk as quickly as possible within a designated hallway for 6 minutes. Participants will be allowed to stop and rest should they feel the need to do so.

Genetic testing- participants will be required to provide proof of A3243G carrier status. Genetic testing will be provided by this study for obligate carriers (people who are expected to carry the A3243G mutation by evaluation of family pedigree) who do not have documentation of carrier status, under a separate consent.

Questionnaires- standard quality of life questionnaires will be administered during the baseline and 1 month outcome visits.

Study medication: Participants will be randomized to one of two doses of Idebenone or placebo. Participants will not know what they have been randomized to until after the completion of the study. You will take the pills 3 times a day, at meal times for 1 month. You will be instructed how to take the study drug, how to store the study drug, and what to do if any study drug is lost or destroyed. You will be asked to bring back the study drug you have not taken, and all the empty study drug packages at the next visit. The study medication is an experimental drug given under an IND (investigational new drug) license. It has not been approved by the FDA for use outside of a research protocol.

Patient Diary
You will receive a 'diary'. In this diary you will make a note of the study drug you have taken each day. You will be able to write down how you are feeling, if there is any illness, or if you have taken any medication other than the study drug. You will be asked to bring back the diary at the next visit.

Your regular doctor will continue to see you whenever necessary. However, some treatments are not allowed during this study. If the regular doctor prescribes any new medication or physical therapy, you will need to contact the study team before you start taking the new medication or having the physical therapy.

Risks

Risks associated with Idebenone:
As with any medicine, the medication used in this study may cause some side effects. Some may have been described by other patients, some may not be known at the present time. A few patients who have taken idebenone have complained of nausea, having diarrhea, heartburn, stomach discomfort, headache, chest pain, muscle pain, dizziness or disturbance of attention. An allergic reaction can not be ruled out. The study medication may make your urine turn red. However, this is not in any way harmful. During the use of idebenone in past years in many patients, including the elderly, there have been some reports of changes in routine blood tests: a decrease in the number of white blood cells, red blood cells and platelets; an increase in liver function values. Your study doctor will be monitoring these values at every visit, but it is important that you tell your study doctor if you feel weak or ill or about anything you feel might be a side effect, even between visits.

Risks associated with females of childbearing age:
The risk associated with Idebenone during pregnancy are unknown therefore
if you are breastfeeding, pregnant, or planning a pregnancy during the course of the study, you will be unable to participate in the study. The effects of idebenone on an unborn baby are unknown and may be harmful to a fetus. If you are eleven years old or older or have already started having periods, you will be given a pregnancy test before starting this study and at every visit thereafter during the course of the study. Should you become pregnant during the study, you will have to be withdrawn by your doctor.

You need to take safety measures to prevent pregnancy (such as not having sexual intercourse, or using a medically accepted form of contraception) while you are receiving idebenone. If you have

questions about how to avoid pregnancy, talk to your doctor or the researcher and they will provide you with information on contraceptive choices.

Risks associated for males:
To this date, no link has been established between the idebenone use and male reproduction ability.

The EKG, physical and neurological exam, questionnaires, and MRS pose no risk to the participant. The participant may feel bored or nervous during the MRS, and the research staff will provide assistance to the participant. Blood sampling will produce minimal amount of discomfort to the participant and there may be some bruising.

Risks associated with 6 Minute Walk Test:
Risks associated with the 6 Minute Walk Test include but are not limited to: chest pain, intolerable dyspnea (breathing difficulty), leg cramps, staggering, diaphoresis (facial flushing-redness), pale or ashen appearance. The participant will be allowed to stop and rest should the need arise. A physician will be available at all times.

Benefits

Participants may not benefit personally from this study, however, the information obtained will be useful to determine whether Idebenone might be useful in the treatment of MELAS.

Alternative Procedures

You may choose not to take part in this research study and continue with your regular medical care.

Confidentiality

Confidentiality Protection

Any information collected during this study that can identify you by name will be kept confidential. We will do everything we can to keep your data secure, however, complete confidentiality cannot be promised. Despite all of our efforts, unanticipated problems, such as a stolen computer may occur, although it is highly unlikely.

The research file that links your name to the code number will be kept in a locked file cabinet and only the investigator and study staff will have access to the file.

The following individuals and/or agencies will be able to look at and copy your research records:

- The investigator, study staff and other medical professionals who may be evaluating the study,

- Authorities from Columbia University and New York Presbyterian Hospital, including the Columbia University Institutional Review Board ('CUIRB')

- The United States Food and Drug Administration ('FDA') and/or the Office of Human Research

Protections ('OHRP')

- Santhera Pharmaceuticals, the collaborator, and its agents or contractors, together (the sponsor)

- Other government regulatory agencies (including agencies in other countries) if Santhera Pharmaceuticals is seeking marketing approval for new products using data from this research.

Due to correspondence between the travel agency, the study site, and the collaborator, Santhera Pharmaceuticals, there could be an unintentional disclosure of the participant's name to Santhera Pharmaceuticals. The Columbia study team and the travel agency will make every effort to ensure that this information is not disclosed

Research Related Injuries

If you are hurt or become ill during the course of this study, you should contact Dr. Michio Hirano (1-212-305-5880 ext 83971 beeper, 1-212-305-1048 office, cell 1-914-400-4788) and the research coordinator (Kris 1-212-305-5880 ext 80516, 1-212-305-6834 office).

Columbia University will assist you in obtaining medical treatment, including emergency treatment, hospital care and follow-up care if you are injured in this study. If your injuries are a result of any study related procedure or the study medication, you will not be responsible for the cost of medical care. If your injuries are not the result of study related procedures you or your insurance carrier will be billed for the cost of such treatment and will be charged in the usual way. If your carrier denies coverage, Columbia University is under no obligation to pay for the treatment. By providing financial or other assistance, neither Columbia University nor the researchers are stating that they are legally responsible for the injury. Further information regarding compensation for injured research subjects may be obtained from the IRB office.

You do not waive any of your legal rights by signing this form.

Additional Information

If you reduced your CoQ10 dose or discontinued other investigational medications at least 1 month prior to the screening visit, a member of the investigational team will contact you to obtain telephone consent prior to medication change. Please mail in or bring the original consent with you to the screening visit and either fax (1-212-305-0431), or e-mail (ke4@columbia.edu) us a copy of the signed consent.

If you have any questions or concerns about the study, you may contact Dr. Michio Hirano (1-212-305-1048) or Ms. Kris Engelstad(1-212-305-6834).

If you have any questions about your rights as a subject, you may contact:

Institutional Review Board

Columbia University Medical Center

722 West 168th Street, 4th Floor

New York, NY 10032

Telephone: (212) 305-5883

An Institutional Review Board is a committee organized to protect the rights and welfare of human subjects involved in research.

Compensation

Participants will receive $75 per research visit to help cover the cost of personal expenses, such as meals.

Additional Costs

The costs of all study medications and diagnostic tests will be covered by the sponsor. Patient travel will be covered by the research study. Patients will travel to NYC at fair and reasonable costs including, airline, personal auto, train, and bus. Overnight stay at a reasonably cost hotel will be covered by the study. Taxi to and from the airport and hotel will be covered by the research study.

Voluntary Participation

Voluntary participation

Taking part in this study is your choice. You can decide not to take part in or stop being in the study at any time. Your choice will not affect the treatment you receive from doctors and staff at Columbia University Medical Center and New York Presbyterian Hospital.

Additional Information

Statement of consent

I have read the consent form and talked about this research study, including the purpose, procedures, risks, benefits and alternatives with the researcher. Any questions I had were answered to my satisfaction. I am aware that by signing below, I am agreeing to take part in this research study and that I can stop being in the study at any time. I am not waiving (giving up) any of my legal rights by signing this consent form. I will be given a copy of this consent form to keep for my records.

Signature

Principal Investigator

Print Name_____Signature_____Date_____

Study Participant
Print Name_____Signature_____Date_____

Parent/Guardian
Print Name_____Signature_____Date_____

Person Obtaining Consent
Print Name_____Signature_____Date_____

Subject Name
Print Name_____