RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE:	A Phase 2, Multi-Center, Open-Label, Ascending Dose Study on the Efficacy, Safety and Tolerability of Perhexiline in Patients with Hypertrophic Cardiomyopathy and Moderate-to Severe Heart Failure with Preserved Left Ventricular Function
PROTOCOL NO.:	HML-PHX-005 WIRB® Protocol #
SPONSOR:	Heart Metabolics, Ltd.
INVESTIGATOR:	Name
STUDY-RELATED PHONE NUMBER(S):	Phone Number(s) (24-hour number required for studies that are more than minimal risk)

INTRODUCTION

You are being asked to take part in a research study. The purpose of this consent form is to help you decide if you want to take part in the research study.

You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help subjects (people who voluntarily take part in research studies) in the future.
- The main goal of regular medical care is to help each person.
- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Parts of this study may involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- Other parts of this study may involve experimental (investigational) drugs or procedures that are being tested for a certain condition or illness. An investigational drug is one that has not been approved by the United States Food & Drug Administration (FDA).
- After reading the consent form and having a discussion with the research staff, you should know which parts of the study are experimental and which are standard medical care.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.
- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study. Taking part in a research study could affect your current or future insurance coverage.

PURPOSE OF THE STUDY

You are being asked to take part in this study because you have been diagnosed with hypertrophic cardiomyopathy (HCM, which is a thickening of your heart muscles that may make it harder for blood to leave the heart) and heart failure (HF, which is when your heart is not able to pump blood as well as it should) with preserved left ventricular (LV) function (which is a specific part of the heart that appears to have normal muscle function).

The purpose of this study is to test the safety and effectiveness of an investigational drug, perhexiline (referred to throughout this form as PEX, the study drug), in subjects with moderate-to-severe HCM. Investigational means the drug has not been approved by the United States Food and Drug Administration (FDA).

STUDY OVERVIEW

This study will be done at about 10 study centers in the United States. About 33 men and women, 18 years of age and older, will be in the study. Each subject will be in the study for about 24 weeks. Those 24 weeks will be broken up as follows:

- Screening: Up to 4 weeks
- Period 1: 8 Weeks of PEX dosing
- Period 2: 8 Weeks of PEX dosing
- Follow-up: 4 Weeks

PROCEDURES

If you decide you are interested in taking part in the study, you must first read and sign this consent form before any study-related tests or procedures can be done.

Screening Visit

The following tests and procedures will be done to see if you are eligible to take part in this study:

- The study staff will go over the study's requirements and answer any questions you may have.
- The study staff will ask you questions about your health and medical history and demographic information (age, sex, race, and ethnic origin).
- The study staff will ask you to list all the medications that you are taking, including all medications prescribed by a doctor and those that you bought on your own without a doctor's prescription (herbals and over-the-counter).
- A physical exam will be done, including measurement of your weight and vital signs (heart rate, blood pressure, temperature and breathing rate). This does not include a pelvic, breasts or rectal exam.
- You will have three (3) separate electrocardiograms (ECGs). This is a tracing of your heart's electrical activity. You will lie on your back and electrodes (sticky pads) with wires are attached to your chest, wrist and ankles. It takes about 5 minutes to do all 3 ECGs.
- Blood and urine samples will be collected for:
    - Safety lab tests

    - A pregnancy test if you are a woman who is able to become pregnant. The result of the pregnancy test must be negative for you to be able to take part in the study.
    - Blood test for HbA1c levels. HbA1c represents your blood sugar levels.
    - CYP2D6, to see if your body is able to break down (process) the study drug. The CYP2D6 genetic test is an FDA approved test used to help how you will respond to certain medications. For this study, it will help us determine how rapidly the cells in your body can modify the study drug. For this genetic blood test, DNA (genetic material) will be removed from your blood sample. CYP2D6 is deficient in some people and they can be identified with this blood test. If you are deficient in this enzyme, you may not be able to participate in this clinical trial.
- A CPEX (Cardio-Pulmonary Exercise) test will be done which uses a stationary bike or treadmill to measure your body's reaction to exercise. A disease or condition that affects your heart, lungs or muscles will limit how much faster and harder you can exercise. A CPEX test looks at how well your heart, lungs, and muscles are working separately, and also how these systems are working together. You will be closely monitored while doing the CPEX test.

Based on these results, if you meet all of the study requirements, you will move on to Period 1.

Period 1: Baseline Visit (Week 1, Day 1)

If you meet all of the study requirements, you will be scheduled to return to the study center no more than 28 days after the Screening Visit. The following tests and procedures will be done:

- Your weight and vital signs will be measured.
- You will be asked how you are feeling and about any medications you have taken since your last visit.
- Urine sample will be collected for a pregnancy test if you are a woman who is able to become pregnant. The result of the pregnancy test must be negative for you to be able to take part in the study
- You will be asked to complete a 6 minute walking test (6MWT). This test measures how far you can walk in 6 minutes. This is usually done on a measured route or path, like a hallway.
- You will have three (3) separate ECGs.
- You will have your second CPEX test.

Study Drug

If you qualify to take part in the study, you will receive a supply of study drug and instructions on how to store your study drug. Study drug will be taken by mouth once a day in the evenings (between 8:00p.m. and 11:00p.m.) with a glass of water or other non-alcoholic drink for the next 112 days. You will be given a diary to record the number of tablets taken on each day. You will also be asked to record the time you take your study drug the evenings before a visit to the study center.

You will begin taking a 70 mg a day dose of study drug during Period 1; this is 2 tablets per day. You will continue to take 70 mg of study drug each day for 2 weeks. After two weeks, your dose may be adjusted (increased or decreased) based on the results of your blood tests. Dose adjustments may occur every two weeks while you are taking part in the study (or more often, if your study doctor decides this is needed).

You may receive the following doses during Period 1:

- 35 mg; 1 tablet
- 70 mg; 2 tablets
- 105 mg; 3 tablets
- 140 mg; 4 tablets
- 175 mg; 5 tablets
- 210 mg; 6 tablets

You may receive the following doses during Period 2:

- 35 mg; 1 tablet
- 70 mg; 2 tablets
- 105 mg; 3 tablets
- 140 mg; 4 tablets
- 175 mg; 5 tablets
- 210 mg; 6 tablets
- 245 mg; 7 tablets
- 280 mg; 8 tablets

Period 1: Day 7, 8 or 9 (End of Week 1)

After you have taken the study drug for at least 6 days, the following tests and procedures will be done:

- You will be asked how you are feeling and about any medications you have taken since your last visit.
- A blood sample will be collected for PEX-CIS testing. The PEX-CIS assay (test) is an investigational device being used to measure the amount of study drug in your blood at each visit once you start taking study drug. The results of this test will be utilized by your doctor to assist him/her in changing the dose of study drug that you will receive. This device has not been approved by the FDA.
- The study staff will go over study drug storage, dosing and accountability instructions with you.
- The study staff will check that you have enough study drug to take every day that will last until your next scheduled visit.

Period 1 (Weeks 2, 4, 6 and 8) and Period 2 (Weeks 10, 12 and 14)

The following tests and procedures will be done:

- You will be asked how you are feeling and about any medications you have taken since your last visit.
- Your vital signs will be measured.
- Your weight will be measured (Week 8 only)
- You will have 3 separate ECGs.
- A blood sample will be collected for:
    - PEX-CIS testing to measure the amount of study drug in your system
    - Safety lab tests (Week 8 only)

    - HbA1c test (Week 8 only)
- A 6 minute walking test (6MWT)(Week 8 only)
- CPEX testing (Week 8 only)
- The study staff will go over study-drug storage, dosing and accountability instructions with you.
- The study staff will check that you have enough study-drug to take every day that will last until your next scheduled visit.

Period 2 (Week 16)

The following tests and procedures will be done:

- You will be asked how you are feeling and about any medications you have taken since your last visit.
- Your vital signs and weight will be measured.
- You will have 3 separate ECGs.
- A blood sample will be collected for:
    - PEX-CIS testing to measure the amount of study drug in your system
    - Safety lab tests
    - HbA1c test
- A 6 minute walking test (6MWT).
- CPEX testing.
- Study drug will be collected.

Follow-Up Visit

You will return to the study center about 4 weeks after your last dose of study drug.
The following tests and procedures will be done:

- You will be asked how you are feeling and about any medications you have taken since your last visit.
- Your weight and vital signs will be measured.
- You will have 3 separate ECGs.
- A blood sample will be collected for:
    - PEX-CIS testing to measure the amount of study drug in your system
    - Safety lab tests
    - Pregnancy test if you are a woman who is able to become pregnant
    - HbA1c test

You may be provided transportation to and from the site.

RISKS AND DISCOMFORTS

The following side effects have occurred while taking PEX:

Short Term (happens after as little as 24 hours of taking PEX): nausea (feeling sick to your stomach), dizziness (usually for a short time), hypoglycemia (low blood sugar in people who have diabetes) and torsade de pointes (a rare, abnormal heart rhythm that may result in death).

Long Term (usually happens after more than 3 months of taking PEX): peripheral neuropathy (nerve damage in your hands and feet), hepatitis/cirrhosis (liver damage,

inflammation and scarring), extrapyramidal dysfunction (not being able to easily move/movement disorders), muscle weakness and ataxia (loss of control of body movement).

In general, when side effects happen, their severity appears to depend upon the amount of the drug that has built up in the patient's body. Because of this you will be asked to give a blood sample on a regular basis to allow a lab to check what levels of the study drug are in your body; depending on the result your dose of study drug may be increased or decreased. In this way it is expected that the risk of adverse events will be greatly reduced.

7 to 8% of all people taking PEX have side effects that are severe enough that they stop taking it. Most side effects usually happen in the first weeks of taking it. The side effects may be passing and may disappear in two to four weeks. Most of the time, the side effects are not as severe when the dose is reduced, but sometimes PEX must be stopped.
Side effects reported the most often are dizziness (feeling faint) or a "drunken" sensation, gait (walking) disorders, unsteadiness, as well as nausea, vomiting, headache, anorexia (loss of appetite, don't feel hungry) and moderate weight loss (4-8 pounds).

Side effects reported often are moderate (and generally, these are passing) increases of proteins and markers that can be detected in your blood (AST/SGOT, ALT/SGPT, ALP, LDH and bilirubin). Increases in total lipids (cholesterol) and triglycerides, hypoglycemia (low blood sugar) and ECG changes (which are changes in your hearts electrical activity).

Side effects reported less often are general weakness, nervousness (feeling anxious), lassitude (not having any energy), insomnia (unable to sleep), tremors (shaking), paresthesias (general feeling of tingling or pricking) , or changes in libido (sexual desire).

Occasionally, the following more severe side effects happen:

- Peripheral neuropathy: This involves the partial loss of sensation or strength due to PEX's effect on the nerves of the body. It may be associated with numbness or tingling, particularly in the hands and feet.
- Severe hypoglycemia (low blood sugar)
- Hypertriglyceridemia (high fat levels in the blood, which might raise your risk of heart disease).
- Significant weight loss (more than 10% of your weight before taking PEX), which can progress to true cachexia (weakness and wasting of the body due to chronic illness). Polyradiculoneuritis, hypoglycemia and weight loss usually go away when you stop taking PEX.
- Hepatopathology, including some cases of subacute alcoholic type hepatitis (inflammation of the liver). Some people have had cirrhosis (scarring of the liver). The state of the liver before treatment with PEX, the influence of other therapies or etiological factors such as alcohol and viral hepatitis, are not known. In rare cases, hepatic (liver) damage or hypoglycemia (low blood sugar) have led to the death of the person.

PEX is known to sometimes change the electrocardiogram (ECG), and this change is referred to as "QT prolongation". With some drugs, QT prolongation has been associated with an increase in the risk of suffering a fatal heart arrhythmia. PEX has been prescribed in Australia and New Zealand for many years to treat chest pain caused by reduced blood flow to the heart muscle (angina) and this arrhythmia has not been associated with the use of PEX in this setting. Nevertheless, it remains a possible risk which needs to be considered when you are deciding about whether or not to participate in the clinical study. You will undergo heart monitoring

(ECG) during this study to see if QT prolongation occurs, and you may be asked to change dosage or stop taking PEX if QT prolongation is seen.

There may be side effects that are not known at this time.

Reproductive Risks

Taking the study drug may involve unknown risks to a pregnant woman, an embryo, fetus (unborn baby) or nursing infant. Therefore, if you are pregnant, planning to become pregnant or are breastfeeding a child, you cannot take part in this study.

In order to reduce the risk of pregnancy, you must use an effective method of birth control while in this study. If you are already using a method of birth control, the study staff will discuss with you whether your current method of birth control is acceptable.

If, during this study or within 30 days after stopping the study drug, you become pregnant, you should notify the study staff as soon as possible. If you become pregnant during the study, the study drug will be stopped and you will no longer be able to be in this study will end. Information about your pregnancy and its outcome will be collected and used to learn more about the effects of the study drug on pregnancy.

Other Risks

Your condition may not get better or may get worse.

Blood Draws

You may have pain, swelling, or bruising where the needle enters your vein. There may be risk of infection. You may feel dizzy or you may faint. The amount of blood collected during this study is about 85-90mL (about 6 tablespoons).

ECG Risks

Skin irritation is rare but could happen from the electrodes or gel that is used.

CPEX Test Risks

This may cause changes in your blood pressure and heart rate. You may feel short of breath, have tightness in your chest, cramping in your legs or fall. Fainting can happen, and in very rare cases, heart attack or stroke.

Walking Test Risks

This may cause changes in your blood pressure and heart rate. You may fall, get short of breath, and have pain in your legs. Fainting can happen, and in very rare cases, heart attack or stroke.

NEW INFORMATION

You will be told about any new information that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS

Your HCM and HF may improve while you are in this study; however, this cannot be promised. The results of this study may help people with HCM and HF in the future.

COSTS

Heart Metabolics, Ltd. will provide the study drug free of charge during this study. Tests and procedures that are done only for the study will not be billed to you or your insurance company.

You or your insurance company may be billed for:

- Any standard medical care given during this research study.
- [list other costs as necessary]

You may want to talk with your insurance company about its payment policy for standard medical care given during a research study. If your insurance company does not pay, you may be billed for those charges.

You might have unexpected expenses from being in this study. Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include who will pay the costs of treating possible side effects.

PAYMENT FOR PARTICIPATION

You will not be paid for being in this study.

Transportation to and from the site may be provided or you will be reimbursed for your own travel costs.

ALTERNATIVE TREATMENT

If you decide not to take part in this study, there are other choices available. These include: the use of drugs used more commonly in other conditions but which have not been proven to be effective in HCM. Another acceptable course of action would be to do nothing. Ask the study doctor to discuss these alternatives with you. You do not need to be in this study to receive treatment for your condition.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?
The study staff will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits

Who may use and give out information about you?
The study staff, which includes the study doctor.

Who might get this information?
The sponsor of this research. "Sponsor" means any persons or companies that are:

- working for or with the sponsor, or
- owned by the sponsor.

Your information may be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- Governmental agencies to whom certain diseases (reportable diseases) must be reported, and
- Western Institutional Review Board® (WIRB®).

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to see if the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
Yes, but this permission will not stop automatically.
[or]
This permission will be good until [date] *[required in CA, DE, IN, IL, WA, and WI].*

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

CONFIDENTIALITY

Information from this study will be given to the sponsor. "Sponsor" includes any persons or companies that are contracted by the sponsor to have access to the research information during and after the study.

The information will also be given to the U.S. Food and Drug Administration (FDA). It may be given to governmental agencies in other countries where the study drug may be considered for approval. Medical records which identify you and the consent form signed by you will be looked

at and/or copied for research or regulatory purposes by:

- the sponsor
- Medpace, an agent for the sponsor;

and may be looked at and/or copied for research or regulatory purposes by:

- the FDA
- Department of Health and Human Services (DHHS) agencies
- governmental agencies in other countries, and
- Western Institutional Review Board® (WIRB®).

COMPENSATION FOR INJURY

If you are injured or get sick as a result of being in this study, call the study staff immediately. The study staff will provide emergency medical treatment. The sponsor has in place an insurance policy in case you get sick from taking the study drug. If the injury or sickness is not related to the study then your insurance will be billed for any treatments received.

No other payment is routinely available from the study staff or sponsor.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Taking part in this study is voluntary. You may decide not to take part or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any reason, including:

- if you have a side effect from the study drug
- if you need a treatment not allowed in this study
- if you do not follow the study procedures as instructed
- if you do not consent to continue in the study after being told of changes in the research that may affect you
- if you become pregnant, or
- if the study is canceled by the FDA

If you leave the study before the planned final visit, you may be asked by the study staff to have some tests or procedures done so that you leave the study safely.

SOURCE OF FUNDING FOR THE STUDY

The sponsor, Heart Metabolics, Ltd. will pay for this research study.

QUESTIONS

Contact [name] at [number(s)] for any of the following reasons:

- if you have any questions about taking part in this study,

- if you feel you have had a research-related injury or a reaction to the study drug, or
- if you have questions, concerns or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who independently review research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

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.

CONSENT

I have read this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

I authorize the release of my medical and research records for the purpose of this study.
By signing this consent form, I have not given up any of my legal rights.

_____
Subject Name (printed)

_____ _____
Signature of Subject Date

_____ _____
Printed Name of Person Conducting the Informed Consent Discussion Position

_____ _____
Signature of Person Conducting the Informed Consent Discussion Date