CONSENT TO BE IN A RESEARCH STUDY

Study Title: Beta-blockers in Pulmonary Arterial Hypertension – A Phase 2 Double-Blind, Placebo-Controlled, Crossover Study Evaluating the Efficacy and Safety of Carvedilol for Right Ventricular Dysfunction in Pulmonary Arterial Hypertension

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University of Minnesota – Division of Cardiology

Sponsor: This is an investigator-initiated study completely funded by the American Heart Association. The Investigational Drug Services at University of Minnesota will provide the study drug. The manufacture of carvedilol has no role in this study.

INTRODUCTION AND PARTICIPANT SELECTION

This study is being conducted by researchers from the University of Minnesota.

You are invited to participate in a research study of beta-blockers as a potential therapeutic approach for the treatment of right heart failure due to Pulmonary Arterial Hypertension (PAH). You were selected as a possible participant because you are a patient at the Pulmonary Hypertension clinic at the University of Minnesota.

We ask that you read this form and ask any questions you may have before agreeing to be in the study.

STUDY PURPOSE

The purpose of the study is to see if carvedilol can be used as a treatment of right heart failure due to Pulmonary Arterial Hypertension (PAH). Carvedilol is approved by FDA for treating several cardiovascular conditions including high blood pressure and left heart failure, but for this study it is being used off label in an experimental way.

STUDY SIZE

This study will be conducted at the University of Minnesota. A total of 26 people will participate in this research study.

STUDY PROCEDURES

This is a cross over study. Subjects will be randomly assigned to placebo or study drug initially for 6 months and later will switch to the opposite group for additional 6 months.

If you agree to participate in this study, we would ask you to do the following:

Screening, Baseline, and Randomization Visit:
We will carefully monitor your progress by watching the standard clinical tests you have done to manage your condition. These include:

- Obtain written consent
- Medical history
- Physical examination
- Concomitant medications
- Vital signs
- Electrocardiogram
- 6 minute walk test
- Heart Ultrasound
- Blood samples (less than 2 teaspoons) for routine hematology, blood chemistry and brain natriuretic peptide (a measure of heart function)
- Pregnancy test for female of childbearing potential
- Cardiac magnetic resonance imaging for assessment of right ventricular function (right ventricular size, volumes, and ejection fraction)
- Right heart catheterization

In addition, so that we can learn more about your condition, the following tests will be done for the purposes of research and will not be billed to you or your insurance:

- Quality of life assessment with Minnesota living with the heart Failure (MLHF) questionnaire
- Blood samples (2 teaspoons) for measuring catecholamine levels (a measure of activation of autonomic nervous system). This sample will be sent to an outside reference lab for testing.

After obtaining the above procedure, you will be randomly assigned to receive either carvedilol or placebo. Randomization means you will be randomly assigned to a treatment based on chance, like a flip of a coin. Neither you nor the researcher chooses your assigned group. You will have an equal chance of being in either group. You be will be initiated on carvedilol or placebo 3.125 mg orally twice a day. If feasible, the screening and baseline visits will be done together.

Subsequently, you will be evaluated at the University of Minnesota pulmonary hypertension clinic by one of the pulmonary hypertension providers every 2 weeks initially for 3 months and then monthly for additional 3 months. Carvedilol or placebo dose will be increased gradually to 6.25 mg twice a day, 9.375 mg twice a day, and 12.5 mg twice a day at week 4, 8, and 12 as tolerated.

To monitor your progress, the following tests will be done for the purposes of research and will not be billed to you or your insurance at Week 2, week 4, week 6, week 8, week 10, month 4, and month 5:

- Medical history
- Physical examination
- Concomitant medications
- Vital signs

- Electrocardiogram
- Functional class

Week 12
We will carefully monitor your progress by watching the standard clinical tests you have done to manage your condition. These include:

- Medical history
- Physical examination
- Concomitant medications
- Vital signs
- Electrocardiogram
- Functional class
- Blood samples (less than 2 teaspoons) for routine hematology, blood chemistry and brain natriuretic peptide.

The following tests will be done for the purposes of research and will not be billed to you or your insurance:

- 6 Minute walk distance

Month 6
We will carefully monitor your progress by watching the standard clinical tests you have done to manage your condition. These include:

- Medical history
- Physical examination
- Concomitant medications
- Vital signs
- Functional class
- Electrocardiogram
- Heart Ultrasound
  Blood samples (less than 2 teaspoons) for routine hematology, blood chemistry and brain natriuretic peptide.

The following tests will be done for the purposes of research and will not be billed to you or your insurance:

- 6 minute walk test
- Cardiac MRI for assessment of right ventricular function (right ventricular size, volumes, and ejection fraction)
- Quality of life assessment with Minnesota Living with Heart Failure questionnaire
- Right heart catheterization
- Blood samples (an additional 2 teaspoons) for measuring catecholamine levels (a measure of activation of autonomic nervous system). This sample will be sent to an outside reference lab for testing.

After 6 months of treatment, the study drug will be tapered down over two weeks and you will be crossed over to the alternative treatment for 6 additional months with the same schedule described above. Throughout the study, you will be evaluated at the University of Minnesota PH clinic by one of the PH team providers every 2 weeks initially for 3 months and then monthly for additional 3 months in both of the 6-month segments.

STUDY DURATION

Your participation in this study will last 13 months.

At the conclusion of the study at 13-months, all patients will wean off the drug over a 2-week period.

RISKS AND DISCOMFORTS

Most of the procedures performed in this study are part of the routine patient care. The risk associated with right heart catheterization includes: pain, bleeding, pneumothorax (an abnormal collection of air or gas in the pleural space that separates the lung from the chest wall), arrhythmias (a condition in which the heart beats with an irregular or abnormal rhythm), pulmonary artery rupture (a tear in the pulmonary artery due to catheter use), and death. Based on prospective and retrospective analyses, the rate of overall serious adverse events is around 1.1%. To minimize the risk of adverse events, an experienced heart failure cardiologist or interventional cardiologist in the catheterization laboratory will perform the procedure using ultrasound and fluoroscopy guidance.

The risk associated with blood draws includes discomfort, bleeding, or rarely, infection.

The risk associated with carvedilol according to frequency and severity:

Common: Low heart rate, low blood pressure, fluid retention, weakness and fatigue particularly at the start of treatment, dizziness, diarrhea, weight gain, hair loss, and worsening control of blood glucose in patients with pre-existing diabetes mellitus.

Less common and serious: Very rarely fainting, heart block, heart failure during up-titration, low blood platelet count, low white blood cell count, attenuate or mask early symptoms and signs of low blood sugar in patients with pre-exisiting diabetes mellitus, and skin reactions.

Carvedilol should not be discontinued abruptly unless it is associated with serious adverse event as this may lead to an abrut increase in heart rate and blood pressure. Carvedilol should be tapered gradually over 2-4 weeks duration.

There is no adequate clinical experience with carvedilol in pregnant women. Hence, pregnant women are excluded from participating in this trial. Animal studies demonstrated that carvedilol or its metabolites are excreted in breast milk. It is not known whether carvedilol is excreted in human mi1k. Breast-feeding is therefore not recommended during administration of carvedilol.

To lessen the risks associated with carvedilol, we will exclude patients with resting heart rate < 60 beats per minute without a pacemaker, advanced heart block without a pacemaker, systolic blood

pressure < 100 mm Hg, resting hear rate > 110 bpm, or if they have functional class IV symptoms or decompensated right heart failure. Subjects with diabetes mellitus will be instructed to watch for early symptoms and signs of hypoglycemia. You will be closely monitored every 2 weeks initially for 3 months and once a month for the next 3 months. If it is determined that the you are not tolerating the dose well, the study doctor will decrease the dose. If at any time in the study you have a serious adverse event or reaction to the study medication, the study drug will stopped. You will be screened for pregnancy at the time of enrollement. If you become pregnant during the study, the study drug will be stopped and you will be exited from the study. Carvedilol will not be stopped abruptly unless you are having a serious adverse event related to the study drug. Otherwise it will be tapered gradually over 2 weeks.

Carvedilol has been availabe in the market for the last two decades and is commonly used to treat hypertension and left ventricular systolic dysfunction.

As part of this study you will undergo three heart imaging procedures (right heart catheterizations). These procedures involve exposure to ionizing radiation. This radiation exposure is not necessary for your medical care and is for research purposes only. The average amount of radiation that the average person would receive from all of these procedures is approximately seven times that received from natural sources of radiation by a Minnesota resident in one year (3 mSv). This exposure involves minimal risk and is necessary to obtain the research information desired

Risks associated with Placebo
There is no risk associated with taking the placebo treatment during the study as you will be continuing to take the standard FDA approved therapy for your pulmonary hypertension.

BENEFITS

There is no guarantee of direct benefit for participating in this research study.

ALTERNATIVES TO PARTICIPATING IN THIS STUDY

You can choose not to participate in this research study and receive your standard clinical care for the treatment of your pulmonary hypertension.

STUDY COSTS/COMPENSATION

There are no anticipated additional costs for participating in this research study. You will receive a $25 gift at your 6 month visit and 13 month visit as a token of our appreciation for your participation in this research study. We will provide parking voucher for your study visits.

RESEARCH RELATED INJURY

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study physicians know right away.

CONFIDENTIALITY

The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. Due to the nature of clinical trial oversight, some funding and regulatory agencies may have the right to review the records of this study. These include: the study sponsor – The American Heart Association, Food and Drug Administration (FDA), The Office of Human Research Protections (OHRP), and Departments at the University of Minnesota with appropriate regulatory oversight. To these extents, confidentiality is not absolute. Study data will be encrypted according to current University policy for protection of confidentiality.

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

PROTECTED HEALTH INFORMATION (PHI)

Your PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect your current or future relations with the University of Minnesota, the University of Minnesota Medical Center-Fairview, or other Fairview Hospitals & Clinics. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

CONTACTS AND QUESTIONS

The researcher conducting this study is Dr. Thenappan Thenappan. You may ask any questions you have now, or if you have questions later, **you are encouraged to** contact him at 612-626-1991.

You may also call the study coordinator, Gretchen Peichel, RN, at 612-626-6237.

If you have any questions or concerns regarding the study and would like to talk to someone other than the researcher(s), you are encouraged to contact the Fairview Research Helpline at telephone number 612-672-7692 or toll free at 866-508-6961. You may also contact this office in writing or in person at Fairview Research Administration, 2344 Energy Park Drive, St. Paul, MN 55108.

You will be given a copy of this form to keep for your records.

Statement of Consent

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Printed Name_____

Signature of Subject_____

Date: _____

Printed Name of Person Obtaining Consent_____

Signature of Person Obtaining Consent_____

Date: _____