Informed Consent Form
Effect of Ivabradine on Patients With Postural Orthostatic Tachycardia Syndrome
NCT #: NCT03182725
Document Date: March 7, 2020

University of California, San Diego
Consent to Act as a Research Subject

IRB 170694: Effect of Ivabradine on Patients with Postural orthostatic tachycardia syndrome (a double-blind placebo-parallel group trial)

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, MD and colleagues at UC San Diego Health System are conducting a research study sponsored by Amgen to find out more about effect of the drug Ivabradine on patients with postural orthostatic tachycardia syndrome (POTS).

You have been asked to participate in this study because you are 18-65 years old and have been diagnosed with POTS (confirmed with norepinephrine levels greater than 600 pg/ml).

There will be 60 participants at this site, though not all who enroll will meet screening criteria and thus pass the screening phase. Approximately 20 participants will continue on to the treatment phase. 10 participants will be randomly assigned to the study drug group -who will receive Ivabradine- and 10 participants will be randomly assigned to the placebo group -who will receive a placebo pill. Half-way through the study, the participants in both groups will stop the study drug (Ivabradine or placebo) for a 1 week washout period. After this washout, the participants will switch groups (i.e. from Ivabradine to placebo group or from placebo to Ivabradine group) for the remainder of the study.

All the study visits will be conducted at UC San Diego Health System in La Jolla, California in the cardiology clinics and the Altman Clinical and Translational Research Institute (ACTRI).

Since Ivabradine is a potential teratogen (agent that can cause malformation of an embryo), we will enroll women who are not pregnant (as confirmed by pregnancy test) or are using highly effective contraceptive methods during the duration of the study (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly) including:

- Combined hormonal (estrogen and progestogen) contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence
- Infertility

Why is this study being done?

The purpose of this study is to investigate the effects of Ivabradine on patients with POTS. Preliminary data indicates that Ivabradine may improve patient symptoms because it has proven to decrease heart rate.

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

All of the study procedures are part of research and not of standard of care. If you agree to be in this study, the following will happen to you:

1) Visit 1: This will take about 1 hour.
   a) You will be asked to come to the ACTRI for pre-screening.
   b) Blood will be drawn (200 ml from the arm) to assess norepinephrine (NE) levels, orthostatic heartrate will be monitored and a pregnancy test will be administered, if deemed necessary by PI.
2) Visit 2: This will take about 1-2 hours
   a) You will be asked to undergo a baseline tilt table test, orthostatic heart rate monitoring, blood tests and quality of life (QOL) questionnaire.
   b) Additional blood work will be drawn to assess cardiometabolic parameters (CBC, CMP, TSH, T4, BNP)
   c) You will be randomly assigned to the Ivabradine or the placebo group. Neither you nor the researcher(s) will know or can choose the group to which you will be assigned. Your chance of being assigned to the Ivabradine group treatment is 50%.
   d) You will be asked to take a pill (Ivabradine 5 mg or placebo 5 mg) twice a day every day for 1 month.
3) Visit 3: This will take about 1 hour.
   a) You will be asked to undergo orthostatic heart rate monitoring.
   b) Based on your orthostatic heart rate measurements and the PI's assessment, you may be asked to increase or decrease the dose from 5 mg to 7.5 mg or 2.5 mg, respectively. If you are tolerating the drug well at the 5 mg dose, then you will be asked to continue at that dosage without any change.
4) Visit 4: This will take about 1 hour.
   a) You will be asked to complete bloodwork (maximum of 200 ml from the arm) to assess norepinephrine (NE) levels, orthostatic heart rate monitoring, and QOL questionnaire.
   b) There will be a 1 week wash out period during which you will not be consuming the study drug or the placebo.
5) After the one-week washout period, you will be crossed over to the other group for one month.
   a) This means that if you were in the Ivabradine group, you will now be in the placebo group and if you were in the placebo group, you will now be in the Ivabradine group.
   b) You will be asked to consume the cross-over pill for one month.
6) Visit 5: This will take about 1 hour.
   a) You will be asked to complete bloodwork (maximum of 200 ml from the arm) to assess norepinephrine (NE) level, a pregnancy test per PI discretion, and QOL questionnaire.
   b) Orthostatic heart rate will be monitored.
7) Visit 6: This will take about 1 hour.
   a) You will be asked to undergo orthostatic heart rate monitoring.

   b) Based on your orthostatic heart rate measurements and the PI's assessment, you may be asked to increase or decrease the dose from 5 mg to 7.5 mg or 2.5 mg, respectively. If you are tolerating the drug well at the 5 mg dose, then you will be asked to continue at that dosage without any change.
8) Visit 7: This will take about one hour.
   a) You will be asked to complete bloodwork (maximum of 200 ml from the arm) to assess norepinephrine (NE) level and QOL questionnaire.
   b) Orthostatic heart rate will be monitored.
9) All blood samples will be saved and stored securely for future analysis. The samples will be properly labeled with a unique subject code identifier, and no personally identifiable information will be on the samples.
   a) Dr. Taub and the Amgen team will have control of the stored specimens, and they will be responsible for deciding how it will be used. 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. Your samples will be stored in a locked unit which can only be accessed by study personnel. 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.

How much time will each study procedure take, what is your total time commitment, and how long will the study last?

The study will last for 3 months, and there will be 7 in-person visits. Your total time commitment will be about 1-2 hours for each visit. You will be randomized into Ivabradine or placebo group for one month then crossed over to the other group for another month. There is a one week wash-out period before cross over begins. During the duration of the study, there will be 1-4 phone call follow-ups to assess compliance and possible adverse effects.

Ivabradine (the study drug) will only be supplied during the duration of the study. Once the study is completed, the drug will no longer be supplied.

Additionally, the PI may ask you to return for a reevaluation of norepinephrine levels with a blood draw if she has reason to believe that the blood draw was done incorrectly or the results are inaccurate. This would be an additional in-person visit.

What risks are associated with this study?

Participation in this study may involve some added risks or discomforts. These include the following:

1. Ivabradine: some potential risks related to the drug being tested include hypertension (high blood pressure), bradycardia (abnormally low heart action), atrial fibrillation (irregular, often rapid heart rate that commonly causes poor blood flow), luminous phenomena (sensations of enhanced brightness), potential teratogen (agent that causes malformation of an embryo).
2. Blood draw: The risks of taking blood include pain, a bruise at the point where the blood is taken, discoloration, redness and swelling of the vein and infection, and a rare risk of fainting.
3. Tilt table test: Patient will lie flat on a table and straps will be secured. After 15 minutes, the table will be quickly tilted to raise the body to stimulate a change in position like standing. Patient will remain secured and in "standing" position for up to 45 minutes, while being monitored continuously. Only qualified medical professionals will perform this test. There may be an increased risk of prolonged hypotension or tachycardia when in "standing" position. These minor complications improve once the table is returned to the horizontal position.
4. Orthostatic heart rate monitoring: Only qualified medical professionals will perform this test. There may be an increased risk of hypotension or tachycardia upon changing positions from laying down to sitting to standing. Patient will be monitored to avoid such risks and treatment will be provided if necessary to return patient to resting heart rate.
5. Quality of life (QOL) questionnaire: Although there are no known adverse risks, some patients may experience frustration, stress, discomfort, fatigue and boredom. These risks will be addressed by informing you in advance and allowing you to stop or pause the questionnaire at any time if you wish, and resuming when you are ready.
6. Washout Period: This washout period may increase risks of cardiovascular events, such as tachycardia.
7. A potential loss of confidentiality. To minimize this risk, subjects will be assigned to unique subject codes. Only the PI and study coordinator will have access to this information.
8. Unscheduled visits: There may be the possibility of having patients return for unscheduled visits in between the scheduled visits. This would be based on PI discretion and/or if the bloodwork needs to be redrawn due to lab or processing errors.

You will be assigned to a study group at random (by chance). Your assignment is based on chance rather than a medical decision made by the researchers. The study group you are assigned to might not be the group you would prefer to be in. Your assigned study group might also prove to be less effective or have more side effects than the other study groups(s), or other treatments available for your condition.

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.

What are the alternatives to participating in this study?
The alternatives to participation in this study are not to participate. This study is optional.

What benefits can be reasonably expected?
There may or may not be any direct benefit to you from these procedures However, the potential benefit to you may be that of improvement in your POTS symptoms and quality of life. The potential benefit to society may include gaining an understanding of the impact of Ivabradine on patients with POTS. The increased knowledge may lead to the design of more effective therapeutic regimens for POTS.

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 requested to: contact the study coordinator, stop taking the medication provided, and have a final visit with blood drawn.

You will be told if any important new information is found during the course of this study that may affect your wanting to continue.

Can you be withdrawn from the study without your consent?
You may be withdrawn from the study if it is in your best medical interest. You may also be withdrawn from the study if you do not follow the instructions given you by the study personnel.

Will you be compensated for participating in this study?
In compensation for your time and travel, you will receive up to $180 upon successful completion of the study. There are 7 visits total; you will receive $45 at the end of Visits 1, 4, 5, and 7.

Are there any costs associated with participating in this study?
There will be no cost to you for participating in this study. We will provide for parking and the study drug for the duration of the study.

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-HRPP (858-246-4777) for more information about this, to inquire about your rights as a research subject or to report research-related problems.

What about your confidentiality?

Research records will be kept confidential to the extent allowed by law. Your medical record number will be recorded on case report forms that will be kept locked up at all times for the addition of research notes. Your research records will be labeled with a code number. The list that matches your name with the code number will be kept in a locked file in the research team's office. Any research records that identify you will be kept only as paper records in a secure ACTRI 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 and the FDA, and the Federal Office of Human Research Protections.

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.

Who can you call if you have questions?

Dr. Pam Taub and/or her designees, _____ , have explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Dr. Pam Taub at 858-246-2510 during the day, or call 619-290-1252 (pager) after 5:00 PM.

Principal Investigator (UCSD)	Pam Taub, MD	858-246-2497
Study Coordinator (UCSD)	Adena Zadourian, BS Hannah Lo, BS	858-246-2510

You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) to inquire about your rights as a research subject or to report research-related problems.

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.

By signing below, you agree to participate.

_____

Name of subject (print)

_____ _____

Signature of subject **Date**

_____

Name of researcher obtaining consent (print)

_____ _____

Signature of researcher obtaining consent **Date**