

Research Plan

Effect of Ivabradine on Patients With Postural Orthostatic Tachycardia Syndrome

NCT #: NCT03182725

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**UCSD Human Research Protections Program  
New Biomedical Application  
RESEARCH PLAN INSTRUCTIONS**

These instructions are for completing the Research Plan that is available in MS Word format from the [HRPP website](#).

The headings on this set of instructions correspond to the headings of the Research Plan.

General Instructions: Enter a response in for all topic headings.

Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 05/11/2011

**1. PROJECT TITLE**

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

**2. PRINCIPAL INVESTIGATOR**

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**3. FACILITIES**

UCSD Altman Clinical and Translational Research Institution (ACTRI)

UCSD Health System

UCSD School of Medicine

**4. ESTIMATED DURATION OF THE STUDY**

1 year

**5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)**

Postural orthostatic tachycardia syndrome (POTS) occurs in approximately 500,000 Americans, but predominates in women with a 5:1 ratio.<sup>1</sup> Patients with POTS experience debilitating tachycardia upon postural changes such as standing that impairs their quality of life. Tachycardia is clinically defined as a heart rate greater than 100 beats/min; and in POTS patients, the prolonged heart rate increase is greater than 30 beats/min or increases to 120 beats/min within the first ten minutes of a diagnostic tilt table test without postural hypotension<sup>1</sup>. There are currently no effective treatment methods for POTS. However, several studies suggest Ivabradine could be a main treatment option for POTS because Ivabradine specifically inhibits the f-channels (If) within the sinoatrial (SA) node, which slows the heart rate<sup>2</sup>. Currently in the US, Ivabradine is mainly prescribed to treat chronic heart failure. It is well tolerated in patients, but it is not commonly prescribed for POTS. It has been also used for treatment of inappropriate sinus tachycardia with good benefit. We hypothesize that Ivabradine will reduce tachycardia and improve functional status in patients with POTS.

**6. SPECIFIC AIMS**

The major objective of this proof-of-concept study is to gain clinical evidence to utilize Ivabradine as a treatment option for POTS. Preliminary data indicates that such an expectation is possible given the fact that Ivabradine has been proven to decrease heart rate.

We will conduct a randomized double-blind placebo controlled clinical trial with a double cross over design. 20 patients with POTS will receive Ivabradine treatment vs placebo for one month. Then there will be a one-week wash out period prior to the cross over in which patients who received Ivabradine will receive the placebo, and patients who initially were on placebo will now receive Ivabradine. We will compare heart rates in both groups after one-month of intervention. We will assess if Ivabradine mitigates patient symptoms and increases patient adherence. This work will help translate our research on beneficial effects of Ivabradine into a clinically relevant patient population.

We will test this hypothesis by pursuing the following aim:

### **Specific Aim 1: Evaluate the change in heart rate**

*Hypothesis: Ivabradine will reduce tachycardia and improve functional status in patients with POTS.*

We propose to test this hypothesis in a randomized double-blind placebo-controlled with a cross over clinical trial in which otherwise healthy patients diagnosed with POTS will be randomized into Ivabradine or placebo group treatment for one month then crossed over to the other group for another month (one week wash-out period before cross over). Patients will undergo a baseline tilt table test, norepinephrine bloodwork, and quality of life (QOL) questionnaires.

- Primary endpoint:
  - Change in heart rate after one month of Ivabradine intervention compared to baseline.
- Secondary endpoint:
  - Quality of life measured with questionnaires after one month of Ivabradine intervention compared to baseline.

We will assess:

- *Effects on tachycardia (table tilt test)*
- *Orthostatic heart rate monitoring*
- *Symptomatic changes (QOL questionnaire)*

*Results will provide significant understanding of mechanisms that underlie sympathetic hyperactivation and provide a potential avenue for an effective and safe treatment with Ivabradine with the ultimate goal of increasing patient adherence and reducing debilitating patient symptoms.*

## **7. BACKGROUND AND SIGNIFICANCE**

Given that the etiology of POTS is complex, there are currently no Class I recommendations for its treatment. POTS has five pathophysiological subtypes 1) hyperadrenergic, 2) peripheral autonomic denervation, 3) hypovolemic 4) deconditioning, 5) anxiety, and hypervigilance. Among the clinical subtypes, the most common form of POTS is hyperadrenergic (comprising up to 50% of POTS patients)<sup>1</sup>. At the cellular level hyperadrenergic POTS is thought to be associated with an increase in hyperpolarization-activated cyclic nucleotide-gated (HCN) channel expression in the sinus node due to an increase in sympathetic activation<sup>2</sup>. The increased sympathetic activity is also associated with elevated norepinephrine levels from a norepinephrine transporter defect, which may have a genetic component<sup>1</sup>. Ivabradine selectively blocks the HCN channel within the SA node resulting in lower heart rate and we hypothesize that it will be beneficial in lower heart rate in patients with POTS that have upregulation in HCN channel expression.

The current standard of care in establishing the diagnosis of POTS is assessing if there is a significant increase in heart rate upon standing or with a tilt table test. The criteria for an augmented heart rate increase is prolonged heart rate increase of greater than 30 beats/min or an increase to 120 beats/min within the first ten minutes of a tilt table test without postural hypotension.<sup>1</sup> Prior to diagnosis of POTS autonomic neuropathies, central dysautonomias, bedrest deconditioning, and dehydration need to be ruled out.<sup>1</sup>

Currently, there are no Class I recommendations for the treatment of POTS. Class II recommendations include: exercise (level B-R), IV saline for acute decompensation (level E), fludrocortisone and pyridostogmine (level C), increased salt and fluid intake, Midodrine or low dose-beta-blocker (level B), and clonidine or methyldopa (level E) for central hyperadrenergic POTS. Florinef and midodrine are most commonly prescribed for these patients but most do not tolerate the side effects. Florinef increases blood volume by increasing the sensitivity of blood vessels to catecholamines; side effects include but are not limited to supine hypertension, hypokalemia, ankle edema, and congestive heart failure.<sup>4</sup> Midodrine works as an alpha-1 adrenergic agonist that does not cross the blood brain barrier; its side effects include piloomotor reactions, supine hypertension, gastrointestinal issues, and urinary retention.<sup>4</sup> There is a great unmet clinical need for an effective intervention in these patients.

Several case reports have shown that Ivabradine is effective in dramatically lowering heart rate in POTS patients, but none have been performed in a randomized clinical trial setting with a placebo group. For example, Ewan et al documented the significant reduction in heart rate in a 15 year old female patient with POTS as a result of Ivabradine consumption that was accompanied by improvements in fatigue<sup>5</sup> and blood pressure remained stable.

Also, Hersi was able to demonstrate that Ivabradine (5mg twice daily) completely alleviated the symptoms (weakness, palpitations, tingling/coldness in feet) of a 25 year old female patient with POTS.<sup>6</sup> It is noteworthy to mention that when she ran out of the medication, her symptoms returned, but were quickly mitigated when Ivabradine was reinstated. Such reports validate that Ivabradine poses as an effective treatment option for POTS patients.

Additionally, the retro-perspective study conducted by McDonald et al identified and analyzed twenty patients who were prescribed Ivabradine (2.5mg once daily) specifically for POTS; this provided valuable insight for utilizing Ivabradine as a treatment option for POTS.<sup>3</sup> McDonald et al concluded that 55% of patients who continued to take Ivabradine reported a decrease in palpitations and tachycardia episodes and 44% of those patients reported a decrease in fatigue<sup>3</sup>. These improvements in fatigue symptoms are consistent with the findings of Ewan et al. However, 20% of these patients were also taking floninef or midodrine in conjunction with Ivabradine, which may have confounded the true efficacy of Ivabradine. Nonetheless, they were able to show that Ivabradine was well-tolerated in patients with POTS and the adverse side effects were minimal.

Similarly, Sutton et al prescribed Ivabradine (5mg twice daily) to twenty POTS patients and concluded that there were notable benefits in terms of reducing palpitations and vasovagal syncope over the course of eighteen months for eighteen patients; two patients discontinued due to lack of benefit.<sup>2</sup>

Moreover, Barzilai et al performed an open-label trial without a placebo group in which they concluded that a single dose of 7.5mg Ivabradine significantly lowered the heart rate of POTS patients without any adverse side-effects.<sup>7</sup> They also noted that Ivabradine maintained the sympathovagal balance despite the significant difference in heart rates between baseline and treatment; they postulate the dosing may be a contributing factor.

Furthermore, many of these prior studies strongly recommend the need for a randomized double-blind placebo-controlled clinical trial in order to measure the efficacy and effectiveness of only prescribing Ivabradine to patients with POTS. Thus, based on prior studies, the goal of this proposal is to evaluate a potentially effective treatment method for POTS with Ivabradine.

## **8. PROGRESS REPORT**

None.

## **9. RESEARCH DESIGN AND METHODS**

**Overall Study Design.** The clinical trial will be registered under [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Subjects between the ages of 18-65 who have a POTS diagnosis will be enrolled. Specifically, we will enroll patients who have hyperadrenergic POTS as confirmed by norepinephrine (NE) levels > 600 pg/ml. This is a 3-month study with a randomized double-blind placebo controlled cross over design. Subjects will be randomized into one of two groups (Ivabradine or placebo for one-month) then crossed over after a one-week washout period to the other group for one-month. Refer to Figure 1 below for details.

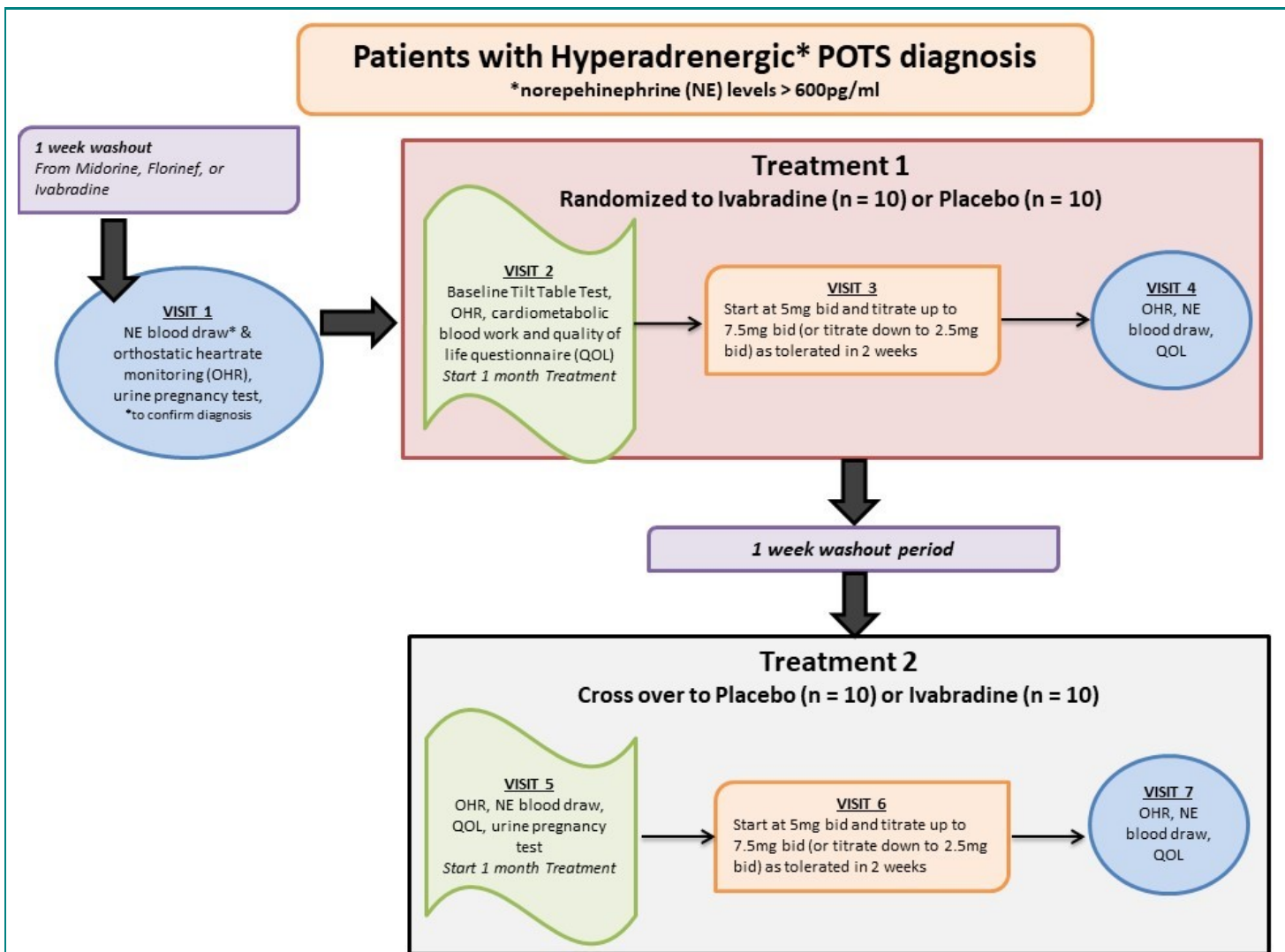


Figure 1. Randomized double-blind placebo-parallel group crossover trial with Ivabradine for patients with POTS.

**Study Visits.** There will be seven visits at the ACTRI and UCSD Cardiology clinics.

-Visit 1 is the pre-screening visit during which norepinephrine (NE) blood results will be obtained to confirm hyperadrenergic POTS diagnosis (NE> 600pg/ml). Orthostatic heart rate will be monitored. A urine pregnancy test will also be administered at this time. Post-menopausal women and women who are infertile will not be asked to take pregnancy test per PI discretion.

-At Visit 2, baseline lab work will be obtained to assess cardiometabolic health (CBC, CMP, TSH, T4, BNP). A tilt table test will be performed to determine baseline heart rate and QOL questionnaire (ShortForm36, SF36) will be completed. Orthostatic heart rate will be monitored. At this point, the patient will be randomized into the Ivabradine or placebo group for one month.

-At Visit 3, two-weeks into treatment, the patient will return to ACTRI for drug titration. Orthostatic heart rate will be monitored. If the patient fulfills criteria (see **Ivabradine Dosing** below), they will either increase, decrease, stop, or not change their Ivabradine dose.

-At Visit 4, one month after starting the current treatment, orthostatic heart rate monitoring, NE bloodwork, and QOL questionnaires will be completed. There will be a one-week wash-out period before the patient crosses over to the other group for one month.

-At Visit 5, the patient will return for orthostatic heart rate monitoring, NE bloodwork, and QOL questionnaires. A urine pregnancy test will be administered at this time. Post-menopausal women and women

who are infertile will not be asked to take pregnancy test per PI discretion. The patient will be instructed to begin the secondary treatment (placebo or Ivabradine) for one month.

-At Visit 6, two-weeks into this treatment, the patient will return to ACTRI for drug titration. Orthostatic heart rate will be monitored. If the patient fulfills criteria (see **Ivabradine Dosing** below), they will either increase, decrease, stop, or not change their Ivabradine dose.

-At Visit 7, one month after starting the secondary treatment, the patient will return for orthostatic heart rate monitoring, NE bloodwork, and QOL questionnaires.

Blood samples will be saved and securely stored with the PI for future research analysis and purposes.

**Randomization.** Randomization refers to the order in which patients receive placebo or Ivabradine. If a patient receives Ivabradine first for one month, then he/she will be switched over to placebo for one month. If a patient receives placebo first for one month, then he/she will be switched over to Ivabradine for one month. There will be a one-week washout period prior to the cross-over. There will be 10 patients in each group.

**Ivabradine Dosing.** Ivabradine dose will initiate at 5mg twice daily (bid) and be increased to 7.5mg twice daily (bid) after 2 weeks<sup>7</sup> if the heart rate is greater than 70 beats/min. If the heart rate is less than 70 beats/min there will no increase in dose. If the heart rate is less than 50 beats/min, or if the patient has symptoms of dizziness or lightheadedness, then Ivabradine will be stopped.

If patients have side effects and feel that cannot continue with Ivabradine we will decrease the dose from 7.5mg bid to 5mg bid (or if they are on 5mg bid to 2.5mg bid). After this dose reduction if the patient is still unable to tolerate Ivabradine, we will stop Ivabradine and withdraw patient from the study. If a patient is unable to tolerate Ivabradine (particularly prior to crossover period), he/she will be withdrawn. The starting dose and titration model is the same for the crossover treatment period as the initial month.

In our clinical experience using Ivabradine in patients with inappropriate sinus tachycardia (which are very similar to POTS patients in age and co-morbidities) we have not seen significant side effects that have caused patients to stop the drug. Refer to the uploaded Ivabradine Drug Information document for more details.

**Specific Protocols.** Brief synopsis of methods currently used is provided below.

**Tilt Table Test:** Only the physician PIs will perform the tilt table test with assistance from the medical staff of the UCSD Medical Center.

**Orthostatic Heart Rate Monitoring:** First, the patient's heart rate will be measured at rest after lying down for 3 minutes. Then, the patient will be asked to stand and the standing heart rate will be measured after 3 minutes. The changes in position with 3 minute intervals will establish the orthostatic heart rate.

**Quality of Life (QOL) Questionnaire:** Patients will complete the Short Form-36 (SF36) subjective questionnaire to aid in analysis of patient symptoms before/after each treatment period.

**Blood Tests:** The following blood tests will be processed at UCSD Clinical Laboratories: 1) Cardiometabolic parameters: (CBC, CMP, TSH, T4, BNP) and 2) norepinephrine levels (NE).

The 2-3-month time period will be used as prior literature suggests that this length of therapy is needed to trigger pharmaceutical changes to translate into functional endpoints.

**Assessments.** We will assess for patient improvement with tilt table testing, orthostatic heart rate monitoring, labs, and quality of life (QOL) questionnaires before and after treatment. The patient will undergo a baseline norepinephrine workup and a baseline tilt table test; if the patient is on Midodrine, Florinef, or Ivabradine, there will be a one week washout period. The patient will then be randomized into the Ivabradine or the placebo group for one month. After this one month, they will undergo orthostatic heart rate monitoring, blood work for norepinephrine levels, and QOL questionnaires. There will be a one week washout period before they are crossed over to the other therapy (placebo vs Ivabradine) for one month. The washout period protocol

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includes maintaining a stable salt and fluid intake. Once crossed over, they will repeat an orthostatic heart rate monitoring, blood work for norepinephrine levels, and QOL questionnaires.

We will continuously assess for all adverse events throughout the study. Some of these labeled adverse reactions may include bradycardia, hypertension, atrial fibrillation, and visual distortions (visual brightness, diplopia, visual impairment, phosphenes).

**Statistical Analysis.** Continuous variables including mean heart rate, maximum heart rate, and quality of life scores will be summarized using descriptive statistics, including the number of observation (n) mean, standard deviation (SD), standard error (SE), median, the 1<sup>st</sup> (Q1) and 3<sup>rd</sup> (Q3) quartiles, minimum, and maximum values. The change in heart rate at one month from baseline will be compared by T-tests based on treatment status with placebo versus Ivabradine. Categorical variables will be compared by McNemar's test based on treatment status with placebo versus Ivabradine.

The study design will be adaptive and data analysis will be done in batches. The PI and others involved in data analysis will be blinded to who is the Ivabradine group and who is in the placebo group.

**Power Analysis.** Assuming a decrease in average heart rate of 10 beats/min is clinically significant (e.g. Decrease from 100 to 90; magnitude of effect 10%) with power 0.8 and standard deviation in heart rate is 7.5 beats/min, the estimated sample size is 18 patients. We will enroll 10 patients in each group to account for the 10% drop-out rate and to ensure the study is adequately powered. For sample size calculation, two-sided alpha level = 0.05 and two sample t-test are used.

**Drop-outs.** If any patient decides to withdraw from the study due to the intolerance of side-effects, we will try to obtain a tilt table test, orthostatic heart rate, QOL questionnaire, and blood tests at the time of drop-out.

**Documentation.** All patient related documentation will be stored at UCSD for future analysis as funding becomes available. To minimize the potential loss of confidentiality, patients will be assigned a unique number as their subject identifier code. The unique subject code will be used to label all study documents. The key that relates the code numbers to the individuals will be kept in a locked cabinet in the PI's office at the ACTRI.

All procedures mentioned above are research procedures and are not part of standard care.

Results may be used for diagnosis, treatment, and prevention of disease in patients.

**Incidental findings that result from the conduct of this study that require medical intervention for the subject will be noted by the PI or her project's medical research staff. They will refer the subject to his primary care physician. If the subject does not have a primary care physician one will be appointed for him or her.**

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## 10. HUMAN SUBJECTS

The study aims for 20 adult volunteers (18-65 years) to complete the study. Given the NE inclusion criteria, we will need to enroll at least 60 participants to have 20 participants pass the study screening criteria. With an expected drop-out of 10% after enrollment, this will provide 18 subjects for final analysis, which provides adequate power to detect a significant improvement in decreasing average heart rate at the 0.05 level (see power analysis, above). Participants will be screened and must meet inclusion and exclusion criteria before they are enrolled into the study. We will recruit patients from the cardiology and internal medicine clinics at UCSD Medical Center; in addition, we will utilize the bioinformatics report generated from EPIC and ResearchMatch to assist in recruitment. The main sites of the clinical testing will be conducted at the ACTRI and UCSD Cardiology clinics.

Inclusion/exclusion criteria are below:

1) Inclusion:

- a. Subjects aged 18-65
- b. Subjects must have POTS diagnosis (Hyperadrenergic Subtype with NE > 600pg/ml)
- c. Subjects with norepinephrine levels greater than 600 pg/ml
- d. Subjects with normal CBC, metabolic, and thyroid levels

2) Exclusion:

- a. Uncontrolled arrhythmias
- b. History of thyroid disease requiring dose titration of thyroid replacement medication(s) within the past 3 months (i.e. hypothyroidism on a stable dose of thyroid replacement therapy is not an exclusion)
- c. Drugs that interfere with Ivabradine (example: Cytochrome P450 drugs).
- d. Presentation of peripheral edema and discolored toes with peripheral autonomic neuropathy. Symptoms include: legs (reduced hair growth, cramps), toes (blue color), legs/feet (wounds, ulcers that do not heal), and muscles (numbness, heaviness).
- e. Subjects who have had a history of systemic illnesses (acute or chronic infectious); active and/or uncontrolled autoimmune/inflammatory disease, COPD, anemia, or diabetes.
- f. History of malignancy undergoing active treatment, except non-melanoma skin cancer.
- g. Uncontrolled psychiatric disorder (including history of hospitalization for psychiatric illness).
- h. Subjects with resting heart rate <60beats/min, atrial fibrillation, advanced AV blocks, sinus disease, and acute decompensated heart failure and severe hepatic impairment.
- i. Smokers or alcohol abuse.
- j. Pregnant or breastfeeding mothers.
- k. Woman of childbearing potential who are unwilling to use highly effective contraception during treatment and for an additional one month after discontinuing the study drug.

Highly effective contraceptive method (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

- 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

If the patient or patient's significant other is infertile, the PI may not require the patient to start other highly effective contraceptive methods in this case as they deem appropriate. The PI shall discuss with the patient and document the decision. The research team will document this in the patient's study file.

For female participants, the PI will administer a pregnancy test at the first visit to determine if patient will be excluded. Another pregnancy test will be administered prior to starting the crossover treatment.

## 11. RECRUITMENT



We aim for 20 adult volunteers with confirmed hyperadrenergic POTS (NE > 600pg/ml) to complete the study. We will screen at least 60 patients in order to have 20 pass the screening phase and complete the study. With an expected drop-out of 10% after enrollment, this will provide 18 subjects for final analysis, which provides adequate power to detect a significant improvement in decreasing average heart rate at the 0.05 level (see power analysis, above). Participants will be screened and must meet inclusion and exclusion criteria before they are enrolled into the study. Additionally, the PI may ask a patient to return for a reevaluation of the baseline screening 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, but it does not increase the risk of the study.

We will recruit from the UCSD Medical Center cardiology and internal medicine clinics. Also, we will be utilizing ResearchMatch and the bioinformatics report from EPIC to help recruit patients who may qualify for our inclusion criteria. Each of these patients will be randomized into one of the two groups mentioned (Ivabradine or placebo).

We will be screening and recruiting patients through UCSD Medical Center clinics. We will also use ResearchMatch, which enables researchers to search for appropriate matches in non-identifiable volunteer profiles. We will be screening patients through EPIC, with the help of their bioinformatics department, for research subjects who might qualify for our criteria. EPIC Bioinformatics will help search for the following to generate a list of potential research subjects:

1. Patient's name, date of birth (DOB), and Medical Record Number (MRN)
2. Patient's primary care provider (PCP) name and contact information
3. POTS diagnosis
4. NE levels >600pg/dl
5. Ages 18-65
6. Exclusion:
  - a. History of thyroid disease requiring dose titration of thyroid replacement medication(s) within the past 3 months (i.e. hypothyroidism on a stable dose of thyroid replacement therapy is not an exclusion)
  - b. Drugs that interfere with Ivabradine (example: Cytochrome P450 drugs)
  - c. Presentation of peripheral edema and discolored toes with peripheral autonomic neuropathy. Symptoms include: legs (reduced hair growth, cramps), toes (blue color), legs/feet (wounds, ulcers that do not heal), and muscles (numbness, heaviness)
  - d. Subjects who have had a history of systemic illnesses (acute or chronic infectious); active and/or uncontrolled autoimmune/inflammatory disease, COPD, anemia, or diabetes.
  - e. History of malignancy undergoing active treatment, except non-melanoma skin cancer.
  - f. Uncontrolled psychiatric disorder (including history of hospitalization for psychiatric illness).
  - g. Subjects with resting heart rate <60beats/min, atrial fibrillation, advanced AV blocks, sinus disease, and acute decompensated heart failure and severe hepatic impairment.
  - h. Smokers or alcohol abuse
  - i. Pregnant women or breastfeeding mothers
  - j. Woman of childbearing potential who are unwilling to use highly effective contraception during treatment and for an additional one month after discontinuing the study drug

After we identify patients of interest for the study, we will contact their primary care provider and get their approval to contact the patient. We will inform clinicians in the department of endocrinology, cardiology family medicine and internal medicine of our study. We will ask these clinicians to ask their patients if they are interested in our study. We will also ask the clinicians to specifically ask the interested patients if it is

acceptable if our research team contacts them. If the patients are interested and give their consent then our study coordinator will either contact them by phone or after their clinic visit.

We will be screening patients prior to informed consent. The following are justifications for partially waiving the HIPAA for screening purposes:

7. It allows the timely review of PHI for patients who are visiting the UCSD clinics, which will allow a greater chance of finding eligible patients. It is imperative that we consent the right patients for the study in order to:
  - a. Reduce the probability of screen failures, and minimize the waste of resources, time and funds.
  - b. Conduct research more smoothly and efficiently, without having to unnecessarily disturb patients who do not qualify for our study.
8. We will be using the partial HIPAA waiver only for the purposes of determining the eligibility of patients, and nothing more. This information can only be determined by screening the patients' medical records on Epic.
9. Screening cannot be practicably conducted without the use of PHI because subject eligibility depends on inclusion and exclusions factors that can only be found in their medical records. The PHI we will be using during the screening process are the patient's age, sex, past medical history, active problems, procedures, images, and medications. Only the PI and the research team will have access to this information.
10. There will be no disclosure of data to anyone outside this research group. PHI will be protected from improper use/disclosure. This will be done by securing the PHI in a locked cabinet in the PI's locked office at the Altman Clinical Translational Research Institute (ACTRI). Only the PI and the research team will have the keys to the office and the cabinet so that only they can review the documents. The PHI will never leave the office or the building.
11. The use of PHI by our research team does not involve more than minimal risk since there are no routine physical or psychological examinations or tests for screening.
12. The research could not be practicably conducted without the waiver since we have to screen the subject prior to recruiting them into the study.
13. The privacy risks are reasonable relative to the anticipated benefits of the research, since the results of the study may improve patient compliance in taking statins, an important drug for cardiovascular disease.
14. If the patient does not qualify, or does not agree to participate in the study, his/her PHI will not be re-used and will be destroyed at the earliest opportunity.

## **12. INFORMED CONSENT**

See attached consent.

Informed consent will be obtained by the study coordinators or research assistants associated with this protocol. Informed consent procedures will be supervised either by the study coordinator, supervising physicians, or the principal investigator. All research personnel giving informed consent will have undergone

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proper training and obtained the required certificates.

The following are justifications for **partially waiving informed consent** for screening purposes:

1. It allows the timely review of PHI for patients who are visiting the UCSD clinics, which will allow a greater chance of finding eligible patients. It is imperative that we consent the right patients for the study in order to:
  - a. Reduce the probability of screen failures, and minimize the waste of resources, time and funds.
  - b. Conduct research more smoothly and efficiently, without having to unnecessarily disturb patients who do not qualify for our study.
2. **Minimal Risk:** The screening procedures are considered minimal risk to the potential subjects because we will be using the partial consent waiver only for the purposes of determining the eligibility of patients, and nothing more. This information can only be determined by screening the patients' medical records on Epic. Screening **cannot be practicably conducted without the use of PHI** because subject eligibility depends on inclusion and exclusions factors that can only be found in their medical records. The PHI we will be using during the screening process are the patient's age, sex, past medical history, active problems, procedures, images, and medications. Only the PI and the research team will have access to this information. There will be no disclosure of data to anyone outside this research group. PHI will be protected from improper use/disclosure. This will be done by securing the PHI in a locked cabinet in the PI's locked office at the Altman Clinical Translational Research Institute (ACTRI). Only the PI and the research team will have the keys to the office and the cabinet so that only they can review the documents. The PHI will never leave the office or the building. The use of PHI by our research team also does not involve more than minimal risk since there are no routine physical or psychological examinations or tests for screening. If the patient does not qualify, or does not agree to participate in the study, his/her PHI will not be re-used and will be destroyed at the earliest opportunity.
3. **Rights and Welfare of Subjects:** The waiver of consent would not adversely affect the rights and welfare of the potential subjects. Their standard of care in the hospital will remain the same regardless of the partial waiver of consent.
4. The potential subject will be informed about the purpose of the study, the duration of the study, the activities they will be doing in the study, the risks and benefits, expenses, compensation, alternatives to participating, privacy, their rights as research subjects and study contact information.
5. The privacy risks are reasonable relative to the anticipated benefits of the research, since the results of the study may improve patient's symptoms and be a potential treatment for POTS.

### **Reconsenting**

In the event that the consent is amended, participants who are active and have not yet completed the study will be informed of these changes and be asked to sign the updated consent form. The updated consent form will be provided to them at an upcoming visit, or through mail, email or fax. They will be given time to review these changes and provide their written consent. They may sign and return it to the research team at the upcoming visit, or through mail, email or fax.

Participants who have completed the study and are no longer active in the study will be made aware of the changes through mail, email or fax. However, these participants will not be asked to acknowledge or confirm the receipt of the updated consent or to sign and return it.

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### 13. ALTERNATIVES TO STUDY PARTICIPATION

Subjects have the right to refuse participation in the study. Patients will have no changes to their current medical regimen. They can choose to withdraw at any time.

### 14. POTENTIAL RISKS

1. Ivabradine: Labeled side effects include: bradycardia, hypertension, atrial fibrillation, and visual distortions (visual brightness, diplopia, visual impairment, phosphenes).
2. Venipuncture: pain, a bruise at the point where the blood is taken, discoloration, redness and swelling of the vein and infection.
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 participants in advance and allowing them to stop or pause the questionnaire at any time if they wish, and resume when they are ready.
6. Washout Period: The washout period may increase risks of cardiovascular events, such as tachycardia.
7. A potential loss of confidentiality: The UCSD Institutional Review Board (IRB), the FDA, and other government agencies may inspect the study records. To minimize the risk of a potential loss of confidentiality, subjects will be assigned a unique subject code and their blood samples will be assigned a different unique specimen code. A separate paper document will link patient identifiers with subject codes and specimen codes. This document will be kept in a secure location in a locked cabinet. Only the PI and study coordinator will have the key to the cabinet. No research documents will have any patient identifiers and will only be labeled with the unique assigned subject codes.
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.

### 15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

All subjects are screened with a medical history and physical exam to ensure none has health problems that put them at risk. Subjects will be thoroughly informed as to these potential problems.

Because this is a low risk study, a Data Safety Monitoring Board (DSMB) is not necessary. Instead, a Data Safety Monitoring Plan (DSMP) is provided.

**A DSMB is not needed for this study for various reasons:**

- The study meets the following IND exemption criteria: **The drug product is lawfully marketed in the United States, and the intent was to provide some latitude to modify the marketed version of the drug product for use in the clinical investigation (see attached Supplement to Biomedical Application Research Plan IND Exemption).**
- This is a low risk study assessing the impact of the drug on lowering heart rate in a specific patient population.
- The study does not involve a high-risk intervention or a vulnerable population, so DSMB should not be needed.
- This is a single site study that is **not intended** to evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome.
- This study is **not intended** to compare rates of mortality or major morbidity.
- This study is addressing lesser outcomes, such as improving patient adherence
- The study population is not at an elevated risk of more severe outcomes.

## DATA SAFETY MONITORING PLAN (DSMP)

### Oversight responsibilities

Oversight of the trial is provided by the Principal Investigator (PI), Dr. Taub.

### Monitoring procedures

Dr. Taub assures that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan. Study data are accessible at all times for the PI to review. The PI reviews study conduct such as accrual, drop-outs, protocol deviations on a monthly basis. The PI reviews AEs individually real-time and in aggregate on a weekly basis. The PI reviews serious adverse events (SAEs) in real-time. The PI ensures all protocol deviations, AEs, and SAEs are reported to the IRB according to the applicable regulatory requirements.

### Collection and reporting of SAEs and AEs

For this study, the following standard AE definitions are used:

**Adverse event:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

**Serious Adverse Event:** Any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

AEs are graded according to the following scale:

**Mild:** An experience that is transient, & requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.

**Moderate:** An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

**Severe:** An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale:

**Not related:** The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

**Possibly related:** An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.

**Related:** The AE is clearly related to the study procedures.

AEs are identified immediately after the study procedure. We will have the patient rest for 30 minutes to an hour after the procedure or activity to observe him or her for any AEs. We will follow up with patient the next day and once a week for the following weeks leading up to their next appointment with us. Dr. Taub who is a cardiologist and a team of nurses will always be nearby the patient at the appointment in case an event occurs.

SAEs and specific procedure-associated AEs are reported to the PI, IRB, and Amgen within 24 hours; PI will report to the FDA in a timely manner. In addition, all AEs are reported according to the IRB AE reporting guidelines.

If a patient becomes pregnant during the study or within a month after the study has ended, patient will be advised to inform the PI immediately and to inform her pregnancy doctor. Patient may be withdrawn from study if she becomes pregnant and the use of the drug will be discontinued. For pregnancies and lactation cases, the PI is responsible for asking the patient if they are willing to allow Amgen to collect pregnancy/birth outcome and/or breastfeeding information and the PI will provide patient's response to Amgen. The PI will be held responsible for reporting SAEs in a timely manner. The PI will attempt to assess any relationship between the procedures and adverse events to prevent future incidences.

### **Management of risks to subjects**

#### *Expected AEs*

1. Blood draw
  - a. Hematoma
  - b. Arterial puncture
  - c. Pain
  - d. Nerve damage
  - e. Re-bleeding
  - f. Allergy
  - g. Phlebitis
  - h. Vasovagal reaction
  - i. Anxiety/fear
2. Tilt table test
  - a. Prolonged hypotension
  - b. Increased tachycardia
3. Orthostatic heart rate monitoring
  - a. Acute hypotension
  - b. Increased tachycardia
4. Consuming Ivabradine
  - a. Bradycardia

- b. Hypertension
  - c. Atrial fibrillation
  - d. Luminous phenomena (phosphenes)
5. Washout period
- a. Increased risk for cardiovascular events such as tachycardia

### AE Management

1. Blood Draw:
- a. Prior to enrollment into the study, the patient will be educated on the risks of the blood draw. The phlebotomist will calm the patient beforehand to reduce anxiety/fear and minimize the probability of vasovagal response. Only sterile needles and gauze will be used to prevent allergic reactions and infection. The area of the blood draw will be thoroughly sanitized with an alcohol wipe prior to the needle stick. Care will be used when penetrating the skin with the needle so that there is a minimized risk of punctured artery and damaged nerve. The needle stick will be done swiftly and securely by an experienced phlebotomist in order to reduce pain. Pressure will be applied on the area immediately after the needle stick to minimize the risk of hematoma. The phlebotomist will inform the patient on when and how to undress their puncture site. Dr. Taub, who is a cardiologist, will be overseeing the procedure to check for the patient's vital signs. Dr. Taub's phone number will be given to the patient for any questions or concerns that may arise in the future.
  - b. In the event of an AE that occurs during the appointment, the facility is equipped with trained medical staff (physicians and nurses) who can respond quickly. Should an event occur, Dr. Taub and the nurses will be nearby to administer immediate medical care and send the patient to the nearest hospital. If the AE occurs after the appointment, the patient will be referred for prompt medical attention. The patient will be withdrawn from the study. Dr. Taub will monitor the patient until the problem has been resolved or has stabilized.
2. Tilt table test:
- a. Prior to enrollment into the study, the patient will be educated on the risks of the tilt table test. The physician will calm the patient beforehand to reduce anxiety/fear and minimize the probability of vasovagal response. Dr. Taub, who is a cardiologist, will be conducting and overseeing the procedure to check for the patient's vital signs. Dr. Taub's phone number will be given to the patient for any questions or concerns that may arise in the future.
  - b. In the event of an AE that occurs during the appointment, the facility is equipped with trained medical staff (physicians and nurses) who can respond quickly. Should an event occur, Dr. Taub and the nurses will be nearby to administer immediate medical care and send the patient to the nearest hospital. If the AE occurs after the appointment, the patient will be referred for prompt medical attention. The patient will be withdrawn from the study. Dr. Taub will monitor the patient until the problem has been resolved or has stabilized.
3. Orthostatic heart rate monitoring:

- a. Prior to enrollment, the patient will be informed about the risks of orthostatic heart rate monitoring. The physician will comfort the patient to reduce anxiety/fear in order to minimize the probability of a vasovagal response. Dr. Taub will continuously monitor and oversee the procedure by checking vital signs. The patient may contact Dr. Taub for further questions/concerns.
  - b. In the event of an AE that occurs during the appointment, the facility is equipped with trained medical staff (physicians and nurses) who can respond quickly. Should an event occur, Dr. Taub and the nurses will be nearby to administer immediate medical care and send the patient to the nearest hospital. If the AE occurs after the appointment, the patient will be referred for prompt medical attention. The patient will be withdrawn from the study. Dr. Taub will monitor the patient until the problem has been resolved or has stabilized.
4. Consuming Ivabradine
- a. Dr. Taub, a cardiologist, will give the patients specific instructions on the amount of ivabradine capsules they would need to consume each day. A research person will follow up with the patient the next day and once a week for the next 90 days to assess the patient's condition. The patient's conditions will be reported back to the PI. If the patients have reasons to believe that Ivabradine is causing any discomfort, consumption of the capsule will be stopped.
  - b. In the event of an AE that occurs during the appointment, the facility is equipped with trained medical staff (physicians and nurses) who can respond quickly. Should an event occur, Dr. Taub and the nurses will be nearby to administer immediate medical care and send the patient to the nearest hospital. If the AE occurs after the appointment, the patient will be referred for prompt medical attention. The patient will be withdrawn from the study. Dr. Taub will monitor the patient until the problem has been resolved or has stabilized.
5. Washout Period
- a. Dr. Taub will monitor the patients closely during this washout period. Dr. Taub will remove patients from the study if it is in their best medical interest. A research person will follow up with the patient once a week during this period to assess the patient's condition. The patient's conditions will be reported back to the PI.
  - b. If an AE occurs, the patient will be referred for prompt medical attention. The patient will be withdrawn from the study. Dr. Taub will monitor the patient until the problem has been resolved or has stabilized.

In the event that a patient either withdraws from the study or the investigator decides to discontinue a patient due to SAE, the patient will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to study medication, or results in death.

#### **Plan for data management**

Data will be collected using standardized paper forms and will only be identified with the study's ID of the participant. The codes that link the name of the participant and the study ID will be kept confidential by the



Principal Investigator in a secured cabinet. Data will be entered in the computer independently by UCSD certificated and trained data entry staff, and discrepancies corrected by a supervisor based on source documents.

Data quality will be monitored by random inspection of the completed forms by the PI. If necessary, re-training of data collectors will be conducted.

## **16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT**

All study forms including consents, HIPAAs, and case report forms (CRFs), which will include elements from the present and past history, patient demographics, including age, current medications and lab draws, will be stored in a locked cabinet in Dr. Taub's office in the ACTRI. Only approved study personnel will have access to this information. To minimize the potential loss of confidentiality, patients will be assigned a unique number as their subject identifier code. The unique subject code will be used to label all study documents.

Collected samples will be saved and securely stored for future analysis. All samples will be labeled with a unique specimen code and the only way to link the specimens with the subject code and any personal health identifiers will be on a physical sheet of paper locked in a cabinet in Dr. Taub's office.

Medical record numbers and social security numbers will be collected only for purposes of subject payment. This information will only be available to study personnel and will be secured in the same manner mentioned above.

## **17. POTENTIAL BENEFITS**

Subjects may or may not benefit directly from participating in the study. The potential benefits to society in general includes an improved understanding of POTS in patients. The increased knowledge may lead to the design of more effective therapeutic regimens for POTS.

## **18. RISK/BENEFIT RATIO**

Ivabradine is an FDA approved drug that has shown many benefits. We expect the benefit to be greater than the potential risks. We believe that risks are minimal in this study.

## **19. EXPENSE TO PARTICIPANT**

There will be no expense to participants. The study drug (Ivabradine) will be provided to enrolled patients at no charge.

## **20. COMPENSATION FOR PARTICIPATION**

Patients will be compensated up to \$180 for fully participating in the study. \$45 will be dispensed at the end of visits 1, 4, 5, and 7 for a total of \$180 upon successful completion of the entire study.

## **21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES**

Dr. Pam Taub is an Associate Professor of Medicine at UCSD and is board certified in internal medicine and cardiology. She has clinical privileges at the VA Medical Center and UCSD Medical Center.

Dr. Jonathan Hsu is an Assistant Professor of Medicine at UCSD and is board certified in internal medicine and cardiology. He has clinical privileges at the UCSD Medical Center.

Michael Wilkinson, MD is a cardiology fellow and will be involved with consenting subjects, as well as participating in data collection and analysis. He is board certified internal medicine and has privileges at UCSD Medical Center.

Jia Shen, MD (Co-Investigator) is an Assistant Professor of Medicine at UCSD and is a board-certified cardiologist. She will assist with the following: patient recruitment, data analysis and manuscript writing.

Iwona Swiatkiewicz, MD, PhD (Co-Investigator) is an Associate Professor of Medicine at Nicolaus Copernicus University and a board-certified cardiologist. She is a visiting scholar who will assist with the following: patient recruitment, data analysis, and manuscript writing.

Adena Zadourian, BS is a research coordinator who will be involved with screening/recruiting/consenting participants, patient visits, administrative support, as well as participating in data collection and analysis. She has undergone proper training and obtained the certificates necessary to work with human subjects.

Hannah Lo, BS is a research coordinator who will be involved with screening/recruiting/consenting participants, patient visits, administrative support, as well as participating in data collection and analysis. She has undergone proper training and obtained the certificates necessary to work with human subjects.

Tiffany Gee, BS is a research assistant who will help with screening/recruiting/ consenting patients, patient visits, and administrative tasks. She has undergone proper training and obtained the certificates necessary to work with human subjects.

Alma Fregoso, BS is a research assistant who will help with screening/recruiting/ consenting patients, patient visits, and administrative tasks. She has undergone proper training and obtained the certificates necessary to work with human subjects.

Christiana Stark, BS is a research assistant who will help with screening/recruiting/scheduling and consenting patients. She will assist with administrative tasks as well. She has undergone proper training and obtained the necessary certificates to work with human subjects.

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## 23. FUNDING SUPPORT FOR THIS STUDY

This study is fully funded by Amgen; Amgen will indemnify.

## 24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

None

## 25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

See uploaded documents.

**26. IMPACT ON STAFF**

None

**27. CONFLICT OF INTEREST**

None

**28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES**

None

**29. OTHER APPROVALS/REGULATED MATERIALS**

None

**30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT**

Only patients who are competent to provide consent will be enrolled in the study.