Using Mirabegron to Increase Blood Pressure in Patients with Postural Orthostatic Tachycardia Syndrome

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Funded by: the American Heart Association

Version Number: 5.0

12 December 2024

Summary of Changes from the Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.1, 1.2, 1.3, 3.0, 9.1	**Addition of QOL questionnaire PROMIS SF 8a**	**This questionnaire is a self-reported measure of physical, mental, and social health in relation to fatigue. We believe this may we one of the mechanisms the study drug, Mirabegron, has had a positive impact on our patient population and would use this questionnaire to evaluate that relationship.**

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

American Heart Association (AHA)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of AHA-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

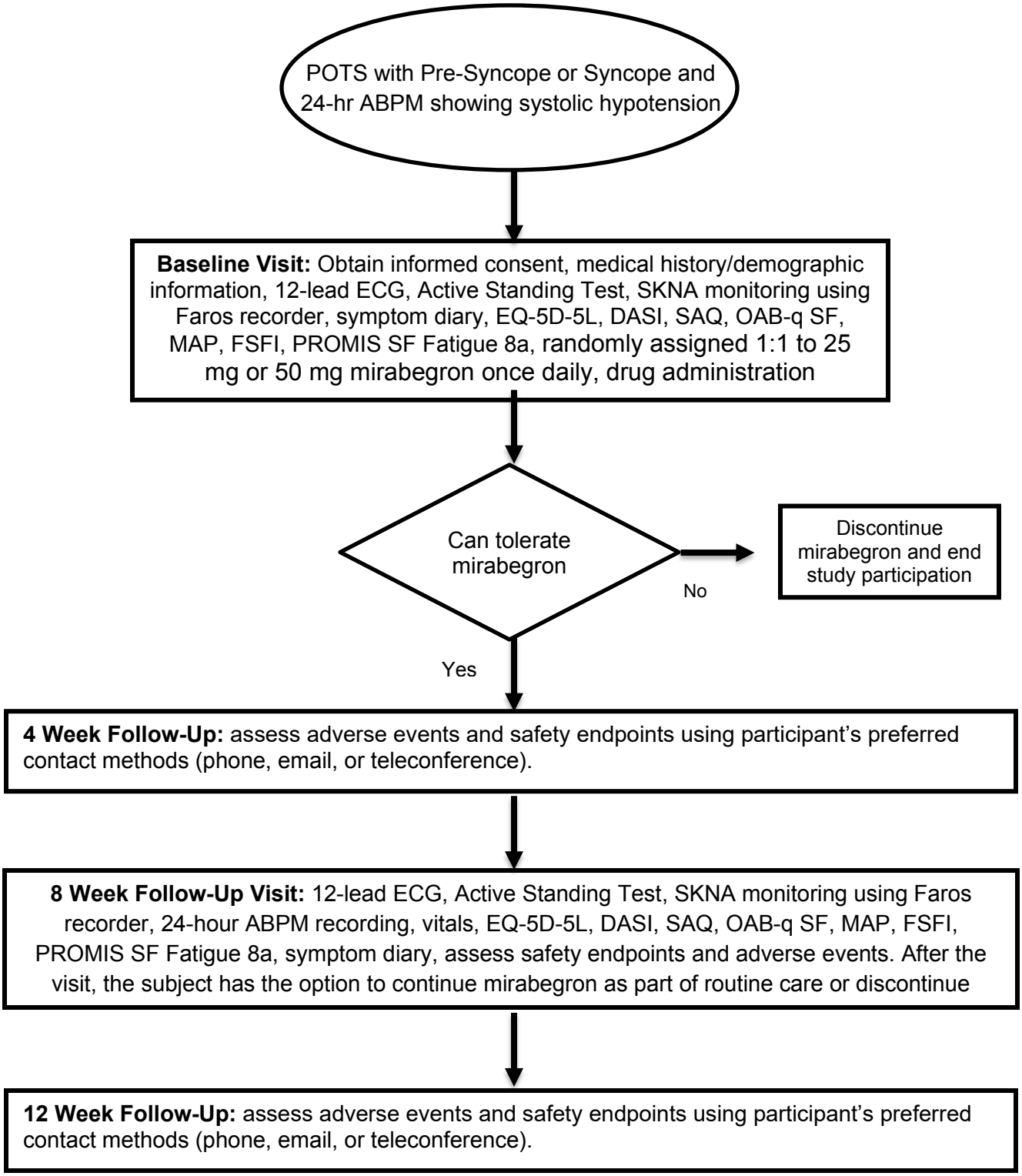
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Using mirabegron to prevent syncope in patients with postural orthostatic tachycardia syndrome
Study Description:	This is a pilot dose-finding study to test the hypothesis that mirabegron increases systolic blood pressure (BP), prevents syncope/presyncope and improves the quality of life (QOL), functional capacity, chest pain, and overactive bladder (OAB) symptoms in patients with *postural orthostatic tachycardia syndrome (POTS)* who have a documented history of hypotension inadequately responsive to conventional treatments. We will perform 24-hr ambulatory blood pressure monitoring (ABPM) and ambulatory skin sympathetic nerve activity (SKNA) recording using a Bittium Faros electrocardiogram (ECG) monitor, assess the number of syncope and presyncope episodes and determine the symptoms using validated questionnaires at baseline. The patients will then be given mirabegron (either 25 mg once daily or 50 mg once daily) for 8 weeks. Afterwards, the patient will return to clinic for clinical assessments, complete questionnaires, ABPM and ambulatory SKNA recording while still on treatment. Mirabegron will be stopped when the data collection is complete. Because mirabegron has a long half-life, we will schedule a video visit with the patient 12 weeks after beginning the treatment and inquire about the patient's symptoms. We will repeat all pertinent questionnaires at that time.

Objectives:	Primary Objective: To test the hypothesis that mirabegron increases systolic BP. Secondary Objectives: To test the hypotheses that mirabegron 1) Prevents syncope/presyncope 2) Improves QOL, functional capacity, chest pain, and OAB symptoms
Endpoints:	Primary Endpoint: - Mirabegron increases the average systolic BP in 24-hr ABPM recording. Secondary Endpoints: - Reduction in frequencies of syncope and presyncope as determined by subject symptom diary - Reduction of the hypotensive (systolic BP < 90 mmHg) episodes during wake time in 24-hr ABPM - Improvement of QOL as measured by the EQ-5D-5L - Improvement of functional capacity as measured by the Duke Activity Status Index (DASI) - Improvement of chest pain as measured by Seattle Angina Questionnaire (SAQ) - Improvement in OAB symptoms as measured by the overactive bladder questionnaire (OAB-q SF) - Improvement of POTS symptom severity as measured by the Malmö POTS Score (MAPS) - Improvement of sexual function in female participants as measured by the Female Sexual Function Index (FSFI) - Improvement of fatigue symptoms as measured by PROMIS SF Fatigue 8a - Reduction of postural heart rate elevation
Study Population:	This pilot study will enroll 20 patients with POTS who have a documented history of hypotension inadequately responsive to conventional treatment.
Phase:	Pilot
Description of Sites/Facilities Enrolling Participants:	The study will enroll patients treated at the Cedars-Sinai Medical Center. This is a single site study.
Description of Study Intervention:	Patients will be randomly assigned 1:1 to receive mirabegron (25 mg or 50 mg once daily) orally for 8 weeks.
Study Duration:	24 months.
Participant Duration:	Approximately 14 weeks.

1.2 SCHEMA


POTS with Pre-Syncope or Syncope and 24-hr ABPM showing systolic hypotension
Baseline Visit: Obtain informed consent, medical history/demographic information, 12-lead ECG, Active Standing Test, SKNA monitoring using Faros recorder, symptom diary, EQ-5D-5L, DASI, SAQ, OAB-q SF, MAP, FSFI, PROMIS SF Fatigue 8a, randomly assigned 1:1 to 25 mg or 50 mg mirabegron once daily, drug administration
Can tolerate mirabegron
No
Discontinue mirabegron and end study participation
Yes
4 Week Follow-Up: assess adverse events and safety endpoints using participant's preferred contact methods (phone, email, or teleconference).
8 Week Follow-Up Visit: 12-lead ECG, Active Standing Test, SKNA monitoring using Faros recorder, 24-hour ABPM recording, vitals, EQ-5D-5L, DASI, SAQ, OAB-q SF, MAP, FSFI, PROMIS SF Fatigue 8a, symptom diary, assess safety endpoints and adverse events. After the visit, the subject has the option to continue mirabegron as part of routine care or discontinue
12 Week Follow-Up: assess adverse events and safety endpoints using participant's preferred contact methods (phone, email, or teleconference).

1.3 SCHEDULE OF ACTIVITIES (SOA)

	Baseline Visit[2]	4 Week Follow-Up (+/- 1 week)[4]	8 Week Follow-Up Visit (+/- 1 week)[3]	12 Week Follow-Up (+/- 1 week)[4]
Screening and eligibility	x			
Obtain informed consent	x			
Medical history/demographics	x			
Concomitant medication review	x			
Vitals	x		x	
12-lead ECG	x		x	
EQ-5D-5L, DASI, SAQ, MAP, FSFI, OAB-q SF, and PROMIS SF Fatigue 8a[8]	x		x	
Ambulatory SKNA recording and symptom diary[5]	x		x	
24-hour ABPM[6]	x[1]		x	
Active Standing Test[7]	x		x	
Study drug dispense	x			
Assess for safety endpoints and adverse events		x	x	x
Subject Parking Validation	x		x	

1. 24-Hour ABPM (conducted as routine clinical care) showing systolic hypotension up to 6 months prior to informed consent will be collected and used as part of Baseline visit study data. In this case, 24-Hour ABPM may not need to be repeated at Baseline visit.
2. Baseline Visit to be conducted in-person in clinic. Informed consent to be obtained in person or virtually through DocuSign. All study activities to be completed in-person, virtually, and/or via mail.
3. 8 Week Follow-Up Visit to be conducted in-person in clinic. 8 Week Follow-Up Visit to occur 8 weeks after the subject begins the mirabegron treatment.
4. 4 Week and 12 Week Follow-Up to be conducted using subjects preferred contact method (phone, email, or teleconference). 4 Week Follow-Up will occur 4 weeks after subject begins initial mirabegron treatment. 12 Week Follow-Up to occur 12 weeks after subject begins initial mirabegron treatment.
5. Ambulatory SKNA recording to be measured for 1-7 days.
6. ABPM recording of at least 24-hours but may be completed for longer than 24-hours.
7. If the patient cannot tolerate the active standing test, it will not be conducted/completed
8. Questionnaires will be administered via REDCap or in person, based on participant preference

2 INTRODUCTION

2.1 STUDY RATIONALE

Chronic orthostatic intolerance syndrome is a disease that often affects multiple organ systems. The cardiovascular involvement leads to the diagnosis of postural orthostatic tachycardia (POTS) or postural syndrome without tachycardia (PSWT).[1] POTS and PSWT are both characterized by chronic (> 3 months) orthostatic intolerance without orthostatic hypotension, but only POTS has > 30 bpm increase of heart rate during active standing test or tilt table test. Hypotension, labile BP, syncope, pre-syncope and severe dizziness are among the most common symptoms suffered by these patients. The prevalence of POTS is approximately 0.2% and affects approximately 500,000 people in the US alone[2, 3] The

prevalence of PSWT is unknown. However, because orthostatic tests are not perfectly sensitive or reproducible, the PSWT patients likely have POTS but did not have documented 30 bpm increase of heart rate during a clinic visit. Since October 2022, the International Classification of Diseases Tenth Edition (ICD-10) added a new code (G90.A) for POTS. That code includes both chronic orthostatic intolerance and postural tachycardia syndrome. For the purpose of the current application, we will use the ICD-10 definition for POTS and recruit patients with chronic orthostatic intolerance, with or without a 30 bpm increase of the heart rate upon standing.

Most patients present between the ages of 15-25 years and over 75% of them are women. Currently available treatment for hypotension is extremely limited. The most commonly used drugs are vasoconstrictors (midodrine and droxidopa). Because of the short half-lives the patients need to take these drugs 3 times daily. The other approach is to use fludrocortisone to increase one's blood volume. Very little clinical trial data are available to document their efficacy in preventing syncope. Therefore, the Heart Rhythm Society consensus statement on POTS does not have a class I recommendation for treatment.[2] Because mirabegron has an excellent long-term safety profile, is well tolerated, and has a very long half-life (50 hours), this therapy could make a large difference in patient's symptoms. If successful, this pilot study may lead to a randomized clinical trial to document the efficacy of mirabegron in treating syncope in patients with POTS or PSWT.

2.2 BACKGROUND

Mirabegron is the first beta-3 receptor stimulator approved by the FDA. The drug is currently indicated in treating OAB. A major off-target effect of this drug is to increase BP. While others have speculated that mirabegron may be useful in treating patients with orthostatic hypotension and dysautonomia,[4, 5] none provided evidence to support that hypothesis. Therefore, the present study is an innovative approach to managing patients with recurrent syncope. Furthermore, mirabegron may also reduce OAB symptoms, which is common in this patient population.

Three patients seen in the PI's POTS clinic responded to mirabegron by increasing BP and eliminating syncope. The first patient is a 69-year old woman referred for orthostatic hypotension and syncope. The patient also suffered from OAB. After treatment with mirabegron for OAB, she had significantly improved BP and no longer had syncope or dizziness. The second patient was referred for syncope, low BP, and POTS. Treatment with mirabegron resulted in stable BP and no syncopal episodes. The third patient is a 20-year-old woman with orthostatic intolerance, labile BP, syncope secondary to orthostatic hypotension, suspected Lupus, and iron deficiency anemia. After receiving mirabegron, patient denied any syncopal episodes and BP improved. The PI has identified other patients with syncope who might benefit from mirabegron. It is possible that mirabegron, by virtue of its stable drug concentration over long periods of time, is effective in preventing the intermittent reduction of the BP as shown in the 24-hour ABPM data, thus prevents syncope. These clinical observations form the basis for this prospective study.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risks associated with the use of mirabegron include hypersensitivity reactions to mirabegron. Use of mirabegron has been associated with increase in BP, urinary retention in patients with bladder outlet obstruction and in patients taking muscarinic antagonist drugs for overactive bladder,

angioedema, and patients taking drugs metabolized by CYP2D6. Most commonly reported adverse reactions were hypertension, nasopharyngitis, urinary tract infection and headache.[6]

CYP2D6 interaction. Mirabegron partly acts as a (quasi-) irreversible, metabolism-dependent inhibitor of cytochrome p450 2D6 *(*CYP2D6*)*.[7] It should not be given to patients who are taking drugs metabolized by CYP2D6. In addition, mirabegron is metabolized by CYP3A and to a minor extent by CYP2D6 in humans.[8] The mirabegron label notes that CYP2D6 poor metabolizers had increased concentrations of the drug as compared to CYP2D6 extensive metabolizers. However, the effect of CYP2D6 phenotype on mirabegron exposure is small and likely of limited clinical importance.[8]

2.3.2 KNOWN POTENTIAL BENEFITS

Mirabegron is a beta-3 activator approved by the United States and the European Union in 2012 to treat patients with OAB syndrome. In 2017, mirabegron was among the top 200 drugs prescribed in the US, with more than one million prescriptions.[9] The safety of mirabegron is well documented by randomized clinical trials that showed the adjudicated cardiovascular events to be comparable for the placebo and mirabegron groups.[10, 11] No adverse events of QTc prolongation or proarrhythmic events were noted. A randomized clinical trial in patients with heart failure showed promising effects on left ventricular ejection fraction and that the treatment is safe and well tolerated.[12] The mechanism of action of mirabegron in OAB is the activation of the detrusor smooth muscle to increase bladder capacity and reduce incontinence. A known off-target (side) effect of mirabegron is the elevation of BP, which may prevent recurrent syncope due to hypotension. If successful, this clinical trial may significantly improve the management of syncope.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Potential benefits

The cardiovascular effects of beta-3 stimulation have been studied in both animal models and humans. The Principal Investigator's lab showed that BRL-37344 (a beta-3 stimulator) effectively suppresses the ventricular tachycardia in a canine model.[13] Dogs receiving BRL-37344 had shorter QTc, lighter heart weight, lower protein levels for sodium calcium exchanger and dihydropyridine receptor and higher beta-3 adrenoceptor expression than the control dogs. There were no changes in beta 1 or beta 2 adrenoceptor expression. A randomized clinical trial in patients with heart failure showed promising effects on left ventricular ejection fraction and that the treatment is safe and well tolerated.[12]

Potential risks

Subjects may experience adverse reactions such as hypertension, nasopharyngitis, urinary tract infection, and headache.

There is a small risk of skin irritation and redness from the ECG electrodes and the skin preparation. The electrode application sites will be checked at time of study exit. The subject's participation in the study will be terminated if the patients develop symptoms or signs of allergy to the electrode, or when the subject voluntarily withdrawal from the study.

The subject may experience slight discomfort with the ABP monitoring system related to continued inflation of the BP cuff. The cuff may also cause skin irritation or a mild rash on the arm that usually goes away after removal of the cuff.

A randomized clinical trial with 50 mg or 100 mg once-daily doses of mirabegron showed no adverse events of QTc prolongation and no proarrhythmic events of ventricular tachycardia, ventricular fibrillation or torsades de pointes.[10] Therefore, we do not think QT prolongation is a potential risk of mirabegron treatment.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective is to test the hypothesis that mirabegron increases systolic BP.	The primary endpoint is the average systolic BP obtained by 24-hr ABPM.	A common side effect of mirabegron is to increase BP. We will use this side effect to manage patients with low BP.
Secondary		
The secondary objective is to test the hypothesis that mirabegron can reduce syncope/pre--syncope, reduce transient hypotensive episodes and improve the QOL.	The secondary endpoints are: 1. Reduction of frequencies of syncope and pre-syncope 2. Reduction of the hypotensive (systolic BP < 90 mmHg) episodes during wake time 3. Improvement of QOL as measured by EQ-5D-5L score 4. Improvement of functional capacity as measured by the Duke Activity Status Index (DASI)	1. Syncope greatly affects the QOL. 2. 20% of the patients with chronic orthostatic intolerance have OAB symptoms. 3. POTS is characterized by large HR elevation upon standing. Reduction of HR elevation during active standing test is a marker of improvement.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	5. Improvement of chest pain as measured by Seattle Angina Questionnaire (SAQ) score 6. Improvement in OAB symptoms as measured by the OAB-q SF 7. Improvement of POTS symptom severity as measured by the MAP 8. Improvement of sexual function in female participants as measured by the Female Sexual Function Index (FSFI) 9. Improvement of fatigue symptoms as measured by PROMIS SF Fatigue 8a 10. Reduce the postural heart rate elevation	

4 STUDY DESIGN

4.1 OVERALL DESIGN

- *A statement of the hypothesis*
  - To test the hypothesis that mirabegron increases BP, prevents syncope/pre-syncope, and improves the QOL and OAB symptoms in patients with POTS.
- *Phase of the trial*
  - Pilot.
- *A description of the type/design of trial to be conducted (e.g., randomized, placebo-controlled, double-blinded, parallel design, open-label, dose escalation, dose-ranging, adaptive, cluster randomized, group sequential, multi-regional, superiority, or non-inferiority design)*
  - This is a dose-ranging pilot study to test the hypothesis that mirabegron increases BP, prevents syncope/pre-syncope, and improves QOL in patients with chronic orthostatic intolerance syndrome.
- *A description of methods to be used to minimize bias*
  - We will explain to the participant that this is a pilot study. The benefit of this drug remains unknown.

- *The number of study groups/arms and study intervention duration*
  - There are two group of patients. The patients are randomly assigned through REDCap to receive either 25 mg/day or 50 mg/day of mirabegron for 8 weeks.
  - Concomitant medication review, QOL and OAB Questionnaires are performed at all timepoints.
  - Assessment of adverse events, 12-lead ECG, 24-hr ABPM, ambulatory SKNA and ECG monitoring are performed at baseline and 8 weeks after the commencement of mirabegron therapy.
- *Indicate if single site or multi-site*
  - This is a single site study.
- *Name of study intervention(s)*
  - Mirabegron, 25 mg or 50 mg orally once daily.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

It is unclear whether the BP elevation effects of mirabegron observed in clinical trials are applicable to patients with syncope or presyncope. All patients will be told that mirabegron has a potential off-target effect of raising BP, but whether it can reduce the frequency of syncope remains unclear. In the QT/QTc healthy volunteer study, the maximum mean increase in supine systolic BP/diastolic BP (SBP/DBP) at a mirabegron dose of 50 mg was ~4.0/1.6 mmHg greater than placebo. The 24-hr average increases in systolic BP versus placebo were 3.0, 5.5, and 9.7 mmHg for the 50, 100, and 200 mg dose groups. Increases in diastolic BP were also dose dependent but were smaller than systolic BP. However, mirabegron has never been tested in the population with hypotension and syncope. It is possible that mirabegron, by virtue of its stable drug concentration over long period of time, is effective in preventing the intermittent reduction of the BP as shown in the 24-hr ABPM measurements even if it has minimal effects on the average BP. In theory, preventing intermittent reduction alone is sufficient to prevent syncope without changing the average BP.

4.3 JUSTIFICATION FOR DOSE

Mirabegron is a new and expensive medication that is approved for use only in adult patients with OAB. This pilot study will inform the development and implementation of future clinical trials because it will allow the investigators to expand the use of mirabegron to patients without OAB. Even in patients with OAB, the insurance company often denies the coverage of mirabegron unless the patients fail other standard OAB drugs. This trial will streamline the use of mirabegron even in patients with OAB. The 25 and 50 mg doses are the most commonly used to treat patients with OAB and have proven to be safe in previous clinical trials.

4.4 END OF STUDY DEFINITION

The end of the study is defined as completion of the last visit and the ABPM/SKNA recording as shown in the Schedule of Activities.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all the following criteria:

1. Provision of signed and dated informed consent form.
2. Age > 18 years old.
3. Documented history of chronic (> 3 months) of orthostatic intolerance.
4. Diagnosis of syncope or pre-syncope and documented intermittent hypotension unresponsive to conventional life-style modification therapy.
    a. A history of syncope (complete loss of consciousness) or presyncope (the sensation that one is about to pass out).
    b. At least one documented hypotensive episode with systolic BP < 90 mmHg on 24-hr ABPM.
    c. Inadequate response to conventional therapies.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients with other potential etiologies of syncope
    a. Sustained tachyarrhythmias other than sinus tachycardia. Specifically, patients with a diagnosis of atrial fibrillation, sustained (> 30 seconds) arrhythmias including paroxysmal supraventricular tachycardia, atrial flutter, ventricular tachycardia, ventricular fibrillation.
    b. Symptomatic bradycardia before pacemaker implantation.
2. Heart failure with either preserved or reduced ejection fraction.
3. Wolff Parkinson-White Syndrome.
4. Stroke within the past 6 months.
5. Any history of myocardial infarction.
6. Active thyrotoxicosis.
7. Any experimental medication concomitantly or within 4 weeks of participation in the study.
8. Patients < 18 years old because mirabegron is not approved by FDA for use in children.
9. People with a history of allergy to ECG electrodes or adhesive tape.
10. Patients with known contraindications or precautions to mirabegron.
    a. Hypertension
    b. Severe renal impairment (calculated CrCl < 30ml/min)
    c. Hepatic disease (Child-Pugh Class B)
    d. Pregnant or lactation
    e. Geriatric patients in long term care facilities
    f. Patients who are known to be allergic to mirabegron
    g. Patients taking drugs that are CYP2D6 substrates. An extensive list can be found at the following website: *https://drug-interactions.medicine.iu.edu/MainTable.aspx*
11. Prisoners

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate but are not eligible to participate. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

- Sample size: 20 subjects – age > 18 years
- Anticipated accrual rate: 2 per month
- All subjects will be enrolled at one US site
- Vulnerable subjects will not be recruited
- All sex, racial and ethnic group members will be recruited to participate in the study

Patients will primarily be recruited through the Cedars Sinai Heart Institute POTS clinic at the time of their office visit. Study brochures will be distributed to physicians' offices and discussed with Cedars-Sinai physicians to help with patient referral and recruitment. We will also include study information in the Smidt Heart Institute Current Research website. Eligible patients will be approached by the investigator and coordinator. The patients will be consented by the investigator or one of the co-investigators utilizing the informed consent form as a guide.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Mirabegron

Mirabegron is a beta-3 adrenergic agonist indicated for the treatment of OAB with symptoms of urge urinary incontinence, urinary urgency, and urinary frequency. A known off-target (side) effect of mirabegron is the elevation of BP, which may be detrimental to patients with hypertension. However, the off-target effect of BP elevation may be exactly what the patients need to prevent recurrent syncope due to hypotension.

6.1.2 DOSING AND ADMINISTRATION

Patients will be randomly assigned to receive mirabegron 25 mg or 50 mg oral once daily. If a dose is delayed or missed for less than 12 hours, the participant will be instructed to take the dose as soon as possible. If the dose the dose is delayed or missed for 12 hours or longer from the scheduled dose, the

participant should skip the dose and take only the next scheduled dose. The participant should document the dose that is skipped, and not take a double dose if a dose is missed.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Mirabegron will be obtained from Cedars-Sinai investigational pharmacy.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Mirabegron is produced by Astellas Pharma US, Inc. The drug is produced as an oval, yellow, film coated tablet, debossed with the Astellas logo. The tablets are labeled “325” for 25 mg dose and “355” for 50 mg dose.

6.2.3 PRODUCT STORAGE AND STABILITY

Mirabegron will be stored per packaging insert guidelines at 25°C with excursions permitted from 15°C to 30°C.

6.2.4 PREPARATION

12-week supply of study drug (Mirabegron) will be dispensed by the Cedars-Sinai investigational pharmacy at baseline visit.

The patient will take the drugs for 8 weeks. The primary and secondary outcomes will be assessed after 8 weeks on the drug. 12 weeks of drug coverage may be needed in case there are scheduling difficulties for follow-up and to allow participants time to obtain the drug themselves if they find it helpful. A 12-week supply was recommended by the pharmacy, as mirabegron comes in 30-count bottles, dispersing the drug for 12 weeks will be easier.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a dose-finding pilot study with 1:1 randomization into two groups of patients receiving either 25 mg or 50 mg dose of mirabegron.

6.4 STUDY INTERVENTION COMPLIANCE

The study team will assess compliance with the study intervention by:

- Maintaining accurate study records and documentation of all required visit tests and procedures
- All research staff will be trained in all study activities
- All research staff will be trained in using the HIPAA compliant REDCap electronic data capture system
- All tests and procedures will be reviewed by a designated research team member
    - Any abnormal result will be reported to the PI immediately

- Patients will be asked to return any remaining medication at the end of the study for accountability

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements. Current medications will be recorded at the baseline visit. Concomitant medications will be reviewed at each visit for accuracy.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from the study drug does mean discontinuation from the study, and remaining study procedures should not be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reasons for discontinuing the study drug
- Any adverse events, serious adverse events, or unanticipated problems

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Study Exit Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced.

Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for any scheduled visits and is unable to be contacted by the study site staff after three attempts.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls, emails, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Procedures/tests/evaluations

- Initial screening process will be conducted via medical chart review and participant interview
- Medical history/demographics will be performed by the investigator
- Concomitant medications will be collected by the research team
- 12-lead ECG and active standing test will be conducted in clinic using standard operating procedures. If participant cannot tolerate the active standing test, it will not be conducted/completed.
- QOL and OAB questionnaires will be administered by the research team in person or via REDCap
- The Faros and ABPM recording devices may be mailed back to the investigator with pre-paid FedEx packaging
- 12-week supply of study drug will be dispensed by the pharmacy. The patient will take the drugs for 8 weeks. The primary and secondary outcomes will be assessed after 8 weeks on the drug.
- Results of study specific procedures will be provided to the participant if deemed medically necessary by the PI and/or co-investigator(s)

8.2 SAFETY AND OTHER ASSESSMENTS

Based on FDA labeling and published literature, mirabegron is expected to have minimal adverse effects. However, patients with POTS have increased probability of having drug allergies. Therefore, safety assessments will be conducted at each study visit. The participant will periodically be assessed for

serious adverse events and unanticipated problems by telephone calls/text message/emails during the 8-week period to assess safety. The study team will communicate with subjects at around 4 weeks to ask how they are doing, are they having any problems, side effects, problems remembering to take the medication. We will ask the participants for their preferred method of communication - telephone call or email. Safety and effectiveness will be assessed at the end of 8 weeks via questionnaires, 7-day ECG monitor, and 24-hour ABPM recording. Because mirabegron has a long half-life, we will do a video conference 4 weeks after drug stoppage to determine if there are any residual side effects.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The principal investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Adverse events (AEs) will be reported to the IRB following IRB guidelines. Sign off on the adverse event will be done in accordance with the IRB guidelines.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the IRB and sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the IRB and sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of

potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

AEs, SAEs, or any significant findings will be reported to the participant by the principal investigator. A follow up letter will be sent to the participant's residence to confirm notification. The PI will coordinate with the patient's physician in managing these AEs and SAEs to ensure patient safety.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

The participant will be withdrawn from the study if they become pregnant.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;

- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor as soon as possible, but no later than 10 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) as soon as possible, but no later than 10 business days of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The PI will inform the patients of unanticipated problems when they occur and again during the routinely scheduled follow up. The PI will coordinate with the patient's physician in managing these unanticipated problems to ensure patient safety.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
  - An increase of the average systolic BP.

- Secondary Efficacy Endpoint(s):
  - Reduction of frequencies of syncope and presyncope
  - Reduction of the hypotensive (systolic BP < 90 mmHg) episodes during wake time
  - Improvement of QOL as measured by EQ-5D-5L score
  - Improvement of functional capacity as measured by the Duke Activity Status Index (DASI)
  - Improvement of chest pain as measured by Seattle Angina Questionnaire (SAQ) score
  - Improvement in OAB symptoms as measured by the OAB-q SF
  - Improvement of POTS symptoms severity as measured by the MAP
  - Improvement of sexual function in female participants as measured by the FSFI
  - Improvement of fatigue symptoms as measured by PROMIS SF Fatigue 8a
  - Reduction of postural heart rate elevation

9.2 SAMPLE SIZE DETERMINATION

This is a pilot study of 20 patients. We did not perform statistical power calculation to determine the sample size.

9.3 POPULATIONS FOR ANALYSES

Patients who completed 8 weeks of therapy will be included in the analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Student's t-tests will be used to compare the mean systolic BP, the QOL and OAB questionnaire scores and the number of syncopal episodes before and after treatment to test the proposed hypotheses.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint is the average systolic BP on 24-hr ABPM recording. This analysis will be conducted on participants who complete 8 weeks of therapy. The systolic BP before and after treatment will be compared with paired Student's t-tests if the data are normally distributed with the Kolmogorov-Smirnov test, or the Shapiro-Wilk test. Wilcoxon signed rank test will be used if the data are not normally distributed. A p-value of ≤ 0.05 will be considered statistically significant.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary endpoints are the QOL score, OAB score and the number of syncopal episodes. This analysis will be conducted on participants who complete 8 weeks of therapy. The data before and after treatment will be compared with paired Student's t-tests. A p-value of ≤ 0.05 will be considered statistically significant.

9.4.4 SAFETY ANALYSES

Safety Endpoints

- Hypertension, defined as any BP measurements of > 140/90 mmHg
- Allergic reaction to mirabegron or skin patch electrodes
- Development of new symptomatic bradycardia or symptomatic 2nd or 3rd degree atrioventricular block
- Development of new symptomatic sustained supraventricular or ventricular tachyarrhythmia

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The data will be summarized by mean and standard deviation.

9.4.6 PLANNED INTERIM ANALYSES

No interim analysis is planned.

9.4.7 SUB-GROUP ANALYSES

No subgroup analysis is planned.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

The baseline and post-treatment data will be listed according to the time points.

9.4.9 EXPLORATORY ANALYSES

None.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol: informed consent, HIPAA form.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator and/or co-investigator(s) will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Cedars-Sinai Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be

identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Cedars-Sinai Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Cedars-Sinai Medical Center.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

All data will be housed in a HIPAA-compliant secure storage system, like REDCap or Box, within the Cedars-Sinai network with access restricted to approved members of the research team. All forms-signed informed consent/authorization forms will be placed in a locked research office and/or file cabinet. The records will be stored indefinitely. Data will be used as preliminary data for future grants and studies.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data Safety Monitor who is a faculty member in the Department of Cardiology. The data safety monitor will meet with the PI every 3 months to review the progress of the study and the safety endpoints. Dr. Bojan Cercek of the Department of Cardiology has agreed to serve as the Data Safety Monitor for this study.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

There is only one site for recruitment. The PI will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and

reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Data collection for REDCap may be completed through review of the medical record and/or the assessment of the clinicians involved in the subject's care. The following data may be collected:

- Demographics
- 12-lead EKG
- Clinic ABPM report
- Diagnoses
- Medications

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the Cedars-Sinai Medical Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations as soon as possible but no later than 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, uploaded to the REDCap database, and reported to AHA and IRB. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

The study will comply with the AHA Data Sharing Policy. The American Heart Association (AHA) requires that all journal articles resulting from AHA funding be made freely available in PubMed Central (PMC) and linked to an AHA award within 12 months of publication. It is the responsibility of the awardee to ensure journal articles are deposited into PMC and that all necessary rights are retained in order to do so.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

ABPM	Arterial Blood Pressure Monitoring
AE	Adverse Event
AHA	American Heart Association
ANCOVA	Analysis of Covariance
BP	Blood Pressure
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DBP	Diastolic Blood Pressure
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DRE	Disease-Related Event
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCS	Neurocardiogenic Syncope
NCT	National Clinical Trial
NIH	National Institutes of Health
OAB	Overactive Bladder
OHRP	Office for Human Research Protections
PI	Principal Investigator
POTS	Postural Orthostatic Tachycardia Syndrome
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SKNA	Skin Sympathetic Nerve Activity
SMC	Safety Monitoring Committee
SNA	Sympathetic Nerve Activity
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
3.0	16 February 2024	**the wording "such as midodrine" was removed**	**Midodrine is not a CYP2D6 substrate, it is a CYP2D6 inhibitor, and therefore this statement is not correct and the drug is not an exclusion. All other CYP2D6 substrates listed at the linked site in this section of the protocol are still valid exclusion criteria**
3.0	16 February 2024	**previously titled "Clinical Monitoring" was removed from the protocol per IRB guidance**	**It is not a condition of our funding and cannot be offered by the IRB at this time. QC will still be implemented and safety oversight completed on a routine basis.**
4.0	24 April 2024	**Addition of active standing test to baseline and week 8 SOA**	**Active standing test is a standard procedure that POTS patients undergo when coming in for a clinic visit and is a data point we would like to collect for comparison between Baseline and Week 8 FU as mirabegron may impact postural heart rate elevation.**
5.0	30 September 2024	**Addition of QOL questionnaires, Malmö POTS Score (MAPS) and Female Sexual Function Index (FSFI), at time of other questionnaires (baseline and week 8 FU)**	**The Malmö POTS Score (MAPS) is a newly developed structured evaluation of symptom severity in patients with POTS. The Female Sexual Function Index (FSFI) is the most widely used questionnaire to evaluate the sexual health in female populations. As POTS affects mostly females and our male participant sample size is too small for analysis on this secondary endpoint, we would like to add only a female-specific sexual function survey. We believe these questionnaires will be beneficial in assessing QOL changes in our study population.**
5.0	30 September 2024	**Use of REDCap survey distribution for questionnaires**	**Due to the volume of questionnaires in the study, offering participants the option of completing the questionnaires online**

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