Rate-Adaptive Atrial Pacing In Diastolic Heart Failure (RAPID-HF)

NCT02145351

30SEP2021

Rate-adaptive Atrial Pacing In Diastolic Heart Failure (RAPID-HF)

A prospective, randomized, double-blind, crossover study of rate adaptive pacing for patients with chronotropic incompetence and heart failure with a preserved ejection fraction.

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Funding Sponsors:	Primary Sponsor: Mayo Clinic 200 First Street SW Rochester, MN 55905 Secondary Sponsor: Medtronic, Inc. 710 Medtronic Pkwy NE, Minneapolis, MN 55432 [redacted]
Study Product:	Dual-chamber pacemaker with rate adaptive pacing Azure XT DR® Pacemaker
Protocol Number: (IRBe)	13-008306

Initial version:[2/27/2014] Version **(1)**
Updated:
07/Jan/2015, Version 2
03/Jun/2016, Version 3: Removed loop diuretic from inclusion criteria.
05/Jul/2016, Version 4: Prior version of protocol had an error in inclusion criteria, where PCWP was listed in criterion #3.4 at 15mmHg and at 20mmHg in criterion #8.2. The modification on 05Jul2016 corrected the PCWP in criterion 8.2 to indicate 15mmHg, the clinical standard used in this patient population.
06/Jun/2017, Version 5: The protocol has been modified to increase the sample size from 30 to 50 to allow for subject drop out, incomplete/inadequate data. We aim to have complete endpoint data for 30 participants. Inclusion/exclusion criteria has been modified to reflect advancements in the current literature. We have clarified study procedures for the randomization visit and additional secondary endpoints. These data are collected through current study procedures, however, they were not included in the protocol as secondary endpoints

01/April/2019, Version 6: Remove Advisa DR pacemaker to the protocol and added Azure XT DR pacemaker.

30/September/2021, Version 8: Change Inclusion Criteria (4.1, Page 13) – Resting PCWP from > 15 to ≥15 mmHG and PCWP/LV end-diastolic pressure from > 25 to ≥ 25 mmHG. Per PI, this was a typo and should be changed to reflect correctly.

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IDE	Investigational Device Exemption
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect

Study Summary

Title	**R**ate-adaptive **A**trial **P**acing **I**n **D**iastolic **H**eart **F**ailure **(RAPID-HF)** A prospective, randomized, double-blind, crossover study of rate adaptive pacing for patients with chronotropic incompetence and heart failure with a preserved ejection fraction.
Running Title	**R**ate-adaptive **A**trial **P**acing **I**n **D**iastolic **H**eart **F**ailure **(RAPID-HF)**
IRB Protocol Number	13-008306
Phase	Pivotal
Methodology	Prospective, randomized, double blind, cross-over study
Overall Study Duration	30 weeks
Subject Participation Duration	20 weeks
Objectives	Assess the effect of rate adaptive pacing on symptoms, exercise capacity, daily activity tolerance, biomarkers and quality of life in patients with chronotropic incompetence and heart failure with a preserved ejection fraction.
Number of Subjects	~~50~~
Diagnosis and Main Inclusion Criteria	Heart failure with ejection fraction ≥ 50% and current symptoms (New York Heart Association II-III), recent hospitalization or need for acute treatment. Chronotropic incompetence, defined as heart rate reserve <0.80 on clinical or screening exercise test within the past 6 months.
Study Device	Dual-chamber cardiac pacemaker, Azure XT DR®, with rate-adaptive pacing of the right atrium. There will be an associated right atrial lead and right ventricular lead.
Duration of Exposure	The device is intended to permanently remain in the body, unless there is a need to remove it.
Reference therapy	The reference is the device with pacing turned off (cross-over design), equivalent to placebo.
Statistical Methodology	The effect of rate-adaptive pacing *on versus off* will be compared within the same individual using paired t-tests for continuous data or McNemar Chi-square test for categorical data.

1 Introduction

This document is a protocol for a human research study to evaluate the effect of rate adaptive atrial pacing in patients with chronotropic incompetence and heart failure with a preserved ejection fraction. This study will be carried out in accordance with the procedures described in this protocol, applicable United States government regulations, good clinical practice standards and Mayo Clinic policies and procedures.

1.1 Background

Heart failure (HF) is the leading cause of hospitalization among Americans >65 years of age, with an annual healthcare cost in excess of $37 billion in 2009.[1] Half of patients with HF have preserved EF (HFpEF) with a left ventricular EF of ≥50%. The prevalence of HFpEF relative to HF with reduced EF (HFrEF) is increasing by 1% per year.[2] In contrast to HFrEF, where 7 drugs/devices have been shown to improve mortality, there is no proven treatment that improves outcomes in HFpEF.[3] Recent clinical trials have tested therapies effective in HFrEF, yet each of these trials has failed to detect a benefit in HFpEF. One possible reason for the failure of prior clinical trials is the complex and heterogeneous pathophysiology of HFpEF, and enrolling patients with different underlying mechanisms into the same study may mask any real benefits.[3–6]

While multiple cardiovascular abnormalities are known to contribute to the pathophysiology of exercise intolerance in HFpEF, chronotropic incompetence (CI) is one consistently observed finding across studies.[7–12] CI is diagnosed during an exercise stress test when a subject is unable to increase their heart rate appropriately to achieve a set percentage of their predicted maximum. Single center studies from our group and others have identified CI in 20-57% of HFpEF patients, and in the recently completed RELAX trial, the prevalence of CI was 77%.[12]

1.2 Investigational Device

There are no investigational devices used in this study. Medtronic Azure XT DR™ is a market-approved dual-chamber pacemaker (pulse generator), Class III Device, Category B. It will be used with atrial and ventricular leads, Medtronic CapSureFix MRI™ model number 5086.

Medtronic Azure XT DR MRI™ model W1DR01 is a permanent, dual-chamber cardiac pacemaker with the ability to continuously monitor and record patient activity, and respond to activity by pacing faster and increasing the heart rate (rate adaptive atrial pacing). It will be programmed in AAIR mode to pace the right atrium.

1.3 Study Rationale and Risk/Benefits

1.3.1 Study Rationale

Heart rate (HR) response to exercise is closely correlated with exercise capacity in HFpEF[9], but it remains unknown whether improving HR responses will translate to improvements in exercise tolerance and quality of life in HFpEF. Guideline statements and review articles frequently recommend HR reduction, rather than higher heart rates in HFpEF.[13] This is based on the idea that a slower HR will increase time available for diastolic filling.

There is some evidence to support this approach. In a human invasive study, Westermann and colleagues reported that stroke volume dropped in HFpEF during atrial pacing (120 bpm)- an effect related principally to a 28% reduction in LV end diastolic volume (LVEDV).[14] However, as pointed out by Kass, this is not an unexpected finding with isolated pacing in healthy people and HF patients.[15] In a separate acute pacing study, Wachter et al. observed less enhancement in LV relaxation velocity (dP/dt_{min}) coupled with reduced stroke volume and end diastolic volumes in HFpEF compared with controls.[16] But again, the relevance of these observations to exercise physiology is unclear, because pacing was not performed during exercise, where venous return is markedly increased. Indeed, in the Westermann study, pacing was also associated with a significant reduction in LV filling pressures in the HFpEF group (16.1 to 7.7 mmHg, $p<0.0001$), and it is possible that if venous return were enhanced (as with exercise), pacing would have been associated with stable filling pressures and stable or even enhanced stroke volume response, which would increase cardiac output and improve exercise capacity.

While it is commonly believed that exercise limitation in HFpEF is predominantly caused by diastolic dysfunction (ventricular filling abnormality),[17] we have recently shown that it is rather inadequate cardiac *ejection reserve* that is the dominant culprit.[7] People with HFpEF display less increase in cardiac output (CO) for any increase in metabolic demand (oxygen consumption, VO_2), with no deficit in the increase in preload volume. The abnormality in CO reserve is caused by both impaired HR and stroke volume (SV) enhancements during exercise.[7] If SV were maintained, an increase in HR would improve CO, but based upon the studies above, it is possible that gains in HR with pacing could be offset by exacerbation of impaired stroke volume reserve from abnormalities in diastolic chamber filling.

Thus while CI is common in HFpEF and is strongly associated with exercise limitation, it remains unknown how restoration of normal HR responses with pacing would affect exercise capacity—in other words, this remains an unanswered fundamental question for which there is currently clinical equipoise.

Permanent pacemaker implantation is approved for the treatment of patients with symptomatic chronotropic incompetence (CI).[18] However, given the concern for impairing diastolic LV filling as suggested by the studies above,[14,16] many or most cardiologists are reluctant to or do not consider referring HFpEF patients for pacemaker implantation.

1.3.2 Anticipated Risks

The main risks associated with this study are from placement of the dual-chamber pacemaker, and the possible adverse effect of employing rate-adaptive pacing in patients with HFpEF.

Pacemaker implantation is routinely performed and study subjects may be exposed to the same risks faced by any patient receiving a pacemaker, which can include:

- Air embolism
- Atrial or ventricular arrhythmias
- Bleeding
- Cardiac perforation, valve damage, and tamponade
- Death
- Failure of the device or leads after placement requiring repeat procedure
- Hematoma or fluid accumulation
- Heart block
- Infection
- Pneumothorax
- Venous thrombosis, stroke, pulmonary embolism
- In placement of the right ventricular lead in a dual-chamber pacemaker system, there may be worsening of tricuspid regurgitation. This risk was carefully considered against the alternative of use a single-lead (atrial only) pacemaker system. However, dual-chamber pacemakers including a ventricular lead are currently standard of care and have been shown to be as safe as single-lead systems.[19] In another study, approximately 2% of patients per year required an additional procedure to place a ventricular lead due to development of AV nodal disease.[20] The presence of atrial fibrillation (AF) also requires the placement of a ventricular lead. A recent study showed that up to two thirds of patients with HFpEF will develop AF at some point in the natural history of the disease.[21]

As discussed previously, there may be possible adverse effects of rate-adaptive pacing in patients with HFpEF related to increasing the heart rate:

- Arrhythmias
- Death
- Inappropriately high pacing rates due to sensor malfunction
- Pulmonary edema
- Worsening heart failure

Possible adverse effects associated with cardiopulmonary exercise (CPX) testing:

- Arrhythmias
- Chest pain and difficulty breathing
- Death
- Heart attack or stroke
- Fainting (syncope) or near-fainting

Every effort has been made to minimize these potential risks through careful study design, patient selection, and close monitoring. The incidence of adverse effects during CPX testing in heart failure patients is low (less than 1%) and is generally safe.[22–24] Our group is also experienced in the conduct of exercise stress tests in patients with HFpEF.

1.3.3 Potential Benefits

We are studying a group of highly symptomatic patients with HFpEF. Pacing may improve exercise capacity, daily activity tolerance, and overall quality of life by reducing fatigue and allowing patients to be more active. Future patients with symptomatic HFpEF with chronotropic incompetence may also benefit from the results of this study. If pacing is found to significantly improve symptoms in HFpEF, without excessive risk, it may become common practice for this population.

2 Study Objectives

This investigation constitutes a pivotal study to assess the effectiveness of rate adaptive pacing (RAP) in subjects with chronotropic incompetence and heart failure with a preserved ejection fraction in a double blind, crossover study design, examining effects on exercise capacity, symptoms, chronic daily activity tolerance, quality of life and neurohormone levels.

We anticipate it will take 20 weeks per patient to complete this study. During this time there will be 6 study visits to Mayo Clinic.

2.1 Objective 1

To determine the effects of rate adaptive atrial pacing on **exercise capacity** in HFpEF. People with HFpEF and chronotropic incompetence (CI) will undergo permanent pacemaker implantation, and exercise capacity will be assessed by expired gas analysis with pacing on or off in a crossover design.

- Our primary hypothesis is that rate-adaptive atrial pacing will improve exercise capacity in HFpEF with CI.
- Our secondary hypotheses are that pacing will reduce symptoms of dyspnea and fatigue during exercise and improve ventilatory efficiency.

2.2 Objective 2

To identify the effects of rate adaptive atrial pacing on **daily activity tolerance** in HFpEF. Activity tolerance will be as assessed by accelerometers contained within the implanted pacemaker device during the pacing-on and off periods. Six minute walk test will be performed with pacing on versus off.

- Our primary hypothesis is that daily activity (minutes active per day assessed by accelerometry) will be greater during the pacing-on period as compared with pacing off.

- Our secondary hypothesis is that 6 minute walk distance will be greater with pacing on compared with pacing off.

2.3 Objective 3

To determine the effects of rate adaptive atrial pacing on **quality of life** and **biomarkers** in HFpEF. People with HFpEF will complete quality of life questionnaires with blood testing with pacing on/off.

- Our primary hypothesis is that quality of life will be improved with pacing on as compared with pacing off.
- Our secondary hypothesis is that NT-proBNP levels will be lower with pacing on versus off.

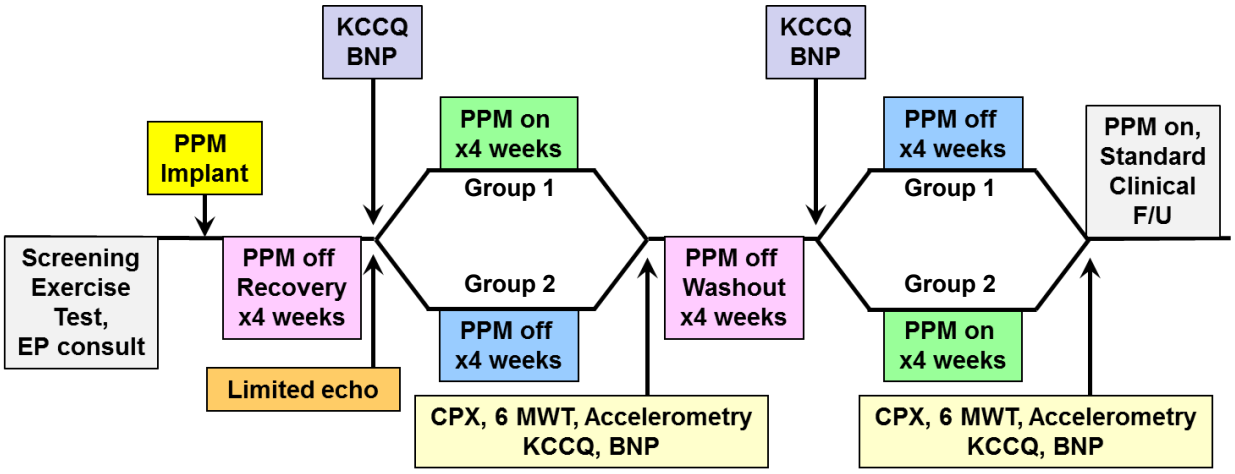
3 Study Design

3.1 General Design

This will be a pivotal study of rate adaptive pacing in patients with HFpEF and CI. It will be a randomized, prospective, double blind, cross-over study. Each participant will have 6 study visits over 20 weeks. After the study, the permanent pacemaker will remain implanted, and the patients will follow-up for standard clinical care with their cardiologist.

We plan to enroll **50 subjects** with HFpEF and CI meeting entry criteria to allow for complete endpoint data in 30.

Study schematic:



3.2 Primary Study Endpoints

Assessment of exercise performance and symptoms (Objective 1)
Volumes of oxygen consumed (VO_2), carbon dioxide produced (VCO_2), breathing frequency (fb), tidal volume (V_T), minute ventilation (V_E), partial pressure of end-tidal oxygen and carbon dioxide ($P_{ET}O_2$ and $P_{ET}CO_2$, respectively) and derived variables (e.g. V_E/VCO_2 slope) will be measured using a low resistance, open-circuit automated metabolic system (Medical Graphics) integrated with a mass spectrometer (Perkin Elmer, model 1100) as previously utilized by our group.[7–9,25] Subjective effort and dyspnea during exercise will be graded by the Borg perceived effort and dyspnea scales.[26] Exercise physiology staff supervising the test (and determining when peak exercise has been achieved) will be blinded to the electrocardiogram to limit potential for bias. Respiratory exchange ratio (RER) will be determined as the ratio of VCO_2/VO_2. VO_2 at anaerobic threshold (VAT) will be determined using the V-slope method. Peak VO_2 will be determined as the final 30 second average at peak exercise.

Assessment of Daily Activity Tolerance (Objective 2)
While peak exercise capacity is a valid, clinically relevant intermediate endpoint in HF trials, it provides relatively little insight into changes in activities of daily living, which are of more concern to the individual patient. The pacemaker devices used in this trial contain accelerometers that provide highly quantitative data (such as hours active each day) and have been used to characterize activity and to assess the impact of interventions on activity levels in patients with other chronic diseases such as COPD, obesity and arthritis.

Quality of life and biomarker assessment (Objective 3)
Quality of life will be assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ).[27] NT-proBNP levels will also be obtained at multiple time points.

3.3 Primary Safety Endpoints

Data will be collected to determine:

- Overall survival
- Hospitalizations for any cause, and for heart failure in particular
- Symptoms of worsening heart failure
- Incidence of all serious adverse events including unanticipated adverse device effects
- Incidence of all device failures and malfunctions

4 Subject Selection, Enrollment and Withdrawal

Patients with HFpEF and chronotropic incompetence will be the target population of this trial. We plan to recruit 50 subjects for this study to allow for complete endpoint data in 30.

4.1 Inclusion Criteria

1. Age >18 years and able to provide informed consent to enroll in the trial, or consent through a legal guardian or power of attorney.
2. Previous clinical diagnosis of HF with current NYHA Class II–III symptoms
3. At least *one* of the following:
    - Hospitalization for decompensated HF
    - Acute treatment for HF with an intravenous diuretic or hemofiltration
    - Chronic treatment with a diuretic for control of HF symptoms + left atrial enlargement or elevated E/e' ratio (≥14 average, ≥15 septal) on echocardiography
    - Resting PCWP ≥15 mm Hg or LV end-diastolic pressure >18 mmHg at catheterization for dyspnea, and/or exercise PCWP/LV end-diastolic pressure ≥25mmHg
    - Elevated NT-proBNP level (≥300 pg/ml)
4. Left ventricular EF ≥40% within 12 months with clinical stability
5. Stable cardiac medical therapy for ≥30 days
6. Sinus rhythm
7. Chronotropic incompetence on recent (within 6 months) clinical exercise test, defined as heart rate reserve (HRR) <0.80 or <0.62 if on beta blockers
    - HRR = [observed peak HR – observed rest HR]/[predicted peak HR – observed rest HR]
    - Predicted peak HR will be calculated using the formula (220-age)
8. Meet both screening criteria on clinically-performed CPX within 12 months
    -

4.2 *Discernable ventilatory anaerobic threshold on previous CPX study.* Exclusion Criteria

1. Inability to exercise, or non-cardiac condition that precludes exercise testing
2. Any contraindication to a pacemaker system
3. Non-cardiac condition limiting life expectancy to less than one year
4. Significant left sided structural valve disease (>mild stenosis, >moderate regurgitation)
5. Hypertrophic obstructive cardiomyopathy
6. Infiltrative or inflammatory myocardial disease (amyloid, sarcoid)
7. Pericardial disease
8. Non-group 2 pulmonary arterial hypertension
9. Chronic stable exertional angina
10. Acute coronary syndrome or revascularization within 60 days
11. Other clinically important causes of dyspnea
12. Atrial fibrillation
13. PR interval >210 msec
14. Resting heart rate (HR) > 100 bpm
15. A history of reduced ejection fraction (EF<40%)
16. Advanced chronic kidney disease (GFR < 20 ml/min/1.73m^2 by modified MDRD equation)

17. Women of child bearing potential without negative pregnancy test and effective contraception
18. Severe anemia (Hemoglobin <10 g/dL)
19. Severe hepatic disease
20. Complex congenital heart disease
21. Listed for cardiac transplantation
22. Other class I indications for pacing

4.3 Subject Recruitment, Enrollment and Screening

Based on previous trials at Mayo Clinic, patients with HFpEF are generally highly motivated to enroll in trials testing novel therapies as there is no established effective treatment for HFpEF. We have an established list of patients with HFpEF who have shown chronotropic incompetence on previous exercise testing and have expressed interest in enrolling in new trials.

Additional patients can be referred from the heart failure clinic. Standard clinical practice will be followed to diagnose and screen patients for possible eligibility for this trial. Patients who meet all of the entry criteria and agree to participate must give written informed consent approved by the investigator's Institutional Review Board (IRB).

Heart failure symptoms such as fatigue and dyspnea on exertion, pulmonary edema, pitting edema will be classified according to the New York Heart Association (NYHA). Those with Class II (symptoms with strenuous activity) or Class III (symptoms with mild activity) heart failure symptoms are eligible for the study.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

A patient may be withdrawn from the study at any time, before or after implantation of the pacemaker, and prior to that subject completing all of the study related procedures. Because of the invasive nature of this study, investigators will do everything possible to avoid withdrawing patients from this study after implantation. Some reasons to withdraw may include:

- Subject safety issues and adverse device effects or complications
- Failure of the subject to adhere to protocol requirements
- Disease progression
- Subject decides to withdraw from the study (withdrawal of consent)

Depending on the time a patient withdraws, investigators may choose to replace that subject with a newly enrolled subject in order to maintain sample size.

In the event of sudden study termination (trial is stopped before completion), patients will be requested to follow-up with their regular cardiologist or at the pacemaker clinic to decide on pacemaker settings.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a patient withdraws from the study for any reason, and cannot or will not complete the investigational aspects of the study, they will be classified as Follow-up Only. They will continue to be seen at visits according to the study protocol, but not necessarily performing tests. The patient will be monitored to capture adverse events, hospitalizations, or medical procedures performed in the term of their expected participation. Implanted pacemakers will be programmed at the discretion of their regular cardiologist.

5 Study Device

The device to be implanted is a dual-chamber cardiac pacemaker manufactured by Medtronic, model Azure XT DR MRI™ with MRI safe leads Medtronic CapSureFix MRI™ model number 5086. They will be provided by Medtronic, Inc. and stored in original marketed packaging until use.

5.1 Description

Permanent pacemaker implantation is approved for treatment of symptomatic sinus node dysfunction with chronotropic incompetence (Class I indication).[18]

We will use the following devices/components:

- Pacemaker pulse generator: Medtronic Azure XT DR MRI™ model W1DR01
- Leads: Medtronic CapSureFix MRI™ model number 5086

All components and devices used in this trial are market-approved and not investigational devices. They will be provided by the manufacturer, Medtronic, and will be the same devices used clinically. Therefore standard clinical practice will be followed for their implantation, programming, and monitoring. Implantation will be performed by a cardiac electrophysiologist.

A pacemaker system is comprised of a pulse generator which contains the battery, electronics and software, and leads which connect it to the heart. The pulse generator is typically inserted underneath the skin of the left upper chest through an incision. The implanting physician will determine the exact location at the time of implant. The pulse generator is connected to a right atrial lead, and a right ventricular lead. These leads are usually inserted into the left subclavian vein and anchored by screwing the tips into the myocardium. The position after placement is confirmed by X-ray.

The pacemaker is able to monitor the electrical activity of the atria and ventricles independently to determine the rhythm and heart rate. The pulse generator also contains an accelerometer that records patient motion. If activity is sensed on the real time accelerometry data, the pacemaker will increase the rate of pacing. The pattern of rate increase and return to baseline will be programmed to achieve a 30 bpm increase in rate with vigorous walking.

This model of pacemaker employs a dual-slope rate response curve that allows two stages of increase for activities of daily living, and active exercise.

Each device (pulse generator and leads) has a manufacturer assigned serial number that will be documented in the patient chart as per routine clinical practice.

5.2 Method for Assigning Subjects to Treatment Groups

Patients will be randomized into two groups using randomization software after the screening visit. One group will start with pacing on, while the other starts with pacing off. They will cross over to the opposite setting midway in the study after the wash out period as outlined in the schematic in section 3.1. Patients and investigators will remain blinded to the programmed status, but the assignment will be kept locked away by the study coordinator if it becomes necessary.

5.3 Preparation and Administration/Implantation of Investigational Device

All participants will receive the same device; there will not be a sham procedure or device. The device should be implanted within 30 days of signing of the informed consent. All implant procedures should be conducted in accordance with the Medtronic physicians manual for the Azure pacemaker system.

The atrial lead will preferably be placed in the high right atrium or atrial septum. The ventricular lead will preferably be placed in the right ventricular apex. The pulse generator is preferably placed in the left pectoral pocket. The implanting physician will perform standard of care testing during the implantation procedure to determine acceptable pacing and sensing thresholds, and later placement will be confirmed on X-ray.

Immediately following completion of the implant, the pacemaker should be set to inactive or minimal pacing modes such as VVI or AAI (50 ppm). Prior to discharge, the pacemaker will be programmed to AAIR mode with a lower rate limit of 50 and the accelerometer set to passive. It will remain in this minimal pacing mode for the next 4 weeks to allow post-op recovery, and collection of baseline sensor and activity data. The Cardiac Compass feature should be enabled to collect data during this period.

5.4 Subject Compliance Monitoring

Once a patient has been randomized and implanted, every effort will be made by the study team to maintain contact with the patient and adhere to scheduled protocol visits and testing procedures over the 20 week participation period. During this time, the study team will keep in contact with the patient to arrange for study visits, and to monitor for adverse events, hospitalizations and overall survival.

If the patient declines to participate further in the study, or changes location, or cannot be contacted or located despite our best efforts, they will be classified as "Lost to Follow Up" and survival will be censored at the last time the patient was known to be alive.

5.5 Prior and Concomitant Therapy

We will collect information on current medications at the baseline visit, including all cardiac medications. In particular, beta-blockers and dosages. There will not be restrictions on medications that can be used during the study.

5.6 Packaging and Labeling

All devices and components to be used in this study are market-approved, and will be obtained from the manufacturer Medtronic in their original packaging. Labeling includes the device model and serial number.

5.7 Blinding of Study

This will be a double-blind study. Patients will be blinded to their randomization assignment and to the pacemaker programming or settings. This will be explained to the patient, and study personnel should not disclose this information to the patient except in the event of a medical emergency. To the fullest extent possible, personnel involved in cardiopulmonary exercise testing should be blinded to the status during the test. Pacer spikes on electrocardiograms should be disabled.

5.8 Receiving, Storage, Distribution and Return

5.8.1 Receipt of Investigational Devices

The pacemaker pulse generator and leads will be obtained from the manufacturer Medtronic. Upon receipt of the devices, inventory and logs will be managed by study personnel to maintain device accountability. Any damaged or unusable devices will be exchanged and documented.

5.8.2 Storage

Pacemakers and leads will be stored in their original packaging at room temperature in containers by study personnel. They will be marked with the required labels and relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings and precautions.

5.8.3 Distribution of Study Device

Pacemaker and leads will be distributed to the implanting physicians and their team before the procedure. The specific serial numbers will be recorded in the patient's chart. Devices will only be distributed immediately before the procedure.

5.8.4 Return or Destruction of Study Device

At routine intervals and at the completion of the study, there will be a reconciliation of devices shipped, devices utilized, and devices remaining. This reconciliation will be logged on the Device Accountability form, signed and dated. Any discrepancies noted will be documented, the sponsor-investigator will be notified and an investigation will be conducted to determine the cause of the discrepancy. Devices destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Visit 1: Screening to determine eligibility + Baseline visit

- The consent form should be reviewed and signed before proceeding with screening
- Patient history will be reviewed for complete medical history, physical examination, EKG, cardiopulmonary exercise testing, a pregnancy test if applicable, review of current medications and NT-proBNP results.
- Prior to implantation, consult with an electrophysiologist to determine eligibility and rule out contraindications to pacing or exclusion criteria (such as preexisting AV nodal disease).

6.2 Visit 2: Pacemaker Implantation

- If patient is eligible, they will undergo implantation with a *Medtronic Azure XT DR MRI*™ dual-chamber permanent pacemaker with MRI compatible atrial and ventricular leads. Placement will be verified on X-ray and the device will be tested to ensure it is functioning correctly.
- Following placement, there will be a 4 week recovery period with the pacemaker off.

6.3 Visit 3: Randomization

- During this visit patients will take their baseline Kansas City Cardiomyopathy Questionnaire (KCCQ), NT-proBNP, and a limited echocardiogram.
- In pacemaker clinic the device function will be verified and patients will undergo a hall walk or treadmill walk to titrate rate responsiveness to achieve about 30 bpm greater HR with pacing during vigorous walking.
- At this visit, half the participants (group 1) will have their pacemakers turned on, while the other half (group 2) will have them off until the next follow-up 4 weeks later.

6.4 Visit 4: Follow-up 1

- At this visit there will be an exercise stress test, a six-minute walk test, a repeat KCCQ, and NT-proBNP.

- Pacemaker function will be checked and both groups will have their pacemakers turned off for 4 weeks for a wash out period.

6.5 Visit 5: Follow-up 2

- At this visit a repeat KCCQ and NT-proBNP will be obtained.
- Pacemaker function will be checked, and then subjects will be switched to the opposite setting. If pacemaker was off at the randomization visit, it will be turned on. If pacemaker was on at the randomization visit, it will remain off.

6.6 Visit 6: Follow-up 3

- Pacemaker function will be checked. They will undergo an exercise test, a six-minute walk test, a KCCQ, and NT-proBNP.
- After the final visit, all patients will have their pacemakers turned on and will follow-up for standard clinical care with their cardiologist.

Schedule of Events Summary

Study Activity	Baseline Screening	2 Implant	3 Randomize	4 F/U 1	5 F/U 2	6 F/U 3
Approximate weeks from baseline	**0**	**4**	**8**	**12**	**16**	**20**
Consent	X					
Review EMR for Inclusion/Exclusion Criteria	X					
Review Medications	X					
Electrophysiology Consult	X					
NT-proBNP			X	X	X	X
Exercise Test				X		X
Pacemaker Implantation		X				
Chest X-Ray		X				
6 Minute Walk Test				X		X
Echocardiogram			X			
Kansas City Questionnaire			X	X	X	X
Hall Walk			X			
Device Programming			X	X	X	X
Device Interrogation Save to Disk		X	X	X	X	X
Record Adverse Events		X	X	X	X	X

7 Statistical Plan

7.1 Sample Size Determination

A power analysis was done in planning for this trial. Based on previous work, we have observed that the standard deviation of the change in ventilator anaerobic threshold (VAT) between two CPX tests in subjects receiving placebo in the RELAX trial was 1.14 ml/kg/min. Assuming this degree of variability, a sample size of 30 subjects will provide 90% power to detect a change in VAT of 0.70 ml/kg/min or greater with pacing, assuming a two-sided significance level of 0.05 in a crossover study design. This detectable difference corresponds to approximately 10% of the baseline mean VAT observed in RELAX. Peak

HR in the RELAX trial was 109±24 bpm, on average 39 bpm below expected peak HR based upon the average age of the population. We expect based upon our algorithm for pacemaker programming (based upon observed vigorous hall walk) that HR at anaerobic threshold will be ~30 bpm greater than resting HR.

7.2 Statistical Methods

Descriptive Statistics

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate for all variables. Baseline values for demographic, clinical, and outcome variables (primary and secondary) will be tabulated for the treatment groups. These analyses will help identify potential confounding variables to be used as covariates in sensitivity analyses.

Handling of Missing Data

Every effort will be made to ensure missing data is kept at a minimum. When entering data into the database, outliers or invalid data will be investigated to check accuracy. Because of the relatively small size of this study, it should be feasible to keep missing data below 5% and avoid the use of imputation.

Multiplicity

No correction will be made for multiple comparisons as we are evaluating a relatively small number of variables.

Objective 1: Determine effects of rate adaptive pacing on exercise capacity
Primary Hypothesis:
VO2 at anaerobic threshold (VAT) within 4 weeks of pacing on is significantly greater than with pacing off.

Comparisons will be made for subjects with pacing set to on versus pacing off. Because these are paired data, statistical comparisons will be made using paired t-tests and McNemar Chi-square test.

Secondary Hypothesis:
Other measures of exercise capacity, including treadmill exercise time, peak VO_2, and V_E/VCO_2 slope, will be improved with pacing on as compared to pacing off. Self-reported symptoms of breathlessness and fatigue during CPX (Borg scores) are lower with pacing on versus off.

Objective 2: Identify effects of rate adaptive pacing on daily activity tolerance
Primary Hypothesis:
Daily activity assessed by average daily minutes active during the 28 day period of pacing-on is greater than with pacing off.

Secondary Hypothesis:
The six minute walk test distance is greater with pacing on vs pacing off.

Objective 3: Determine effects of rate adaptive pacing on quality of life and biomarkers
Primary Hypothesis:
KCCQ scores are higher after 4 weeks of pacing on versus pacing off (indicating improving quality of life)

Secondary Hypothesis:
NT-proBNP levels are lower after 4 weeks of pacing on versus pacing off.

Interim Analysis

There is no plan to conduct an interim analysis or stop early. This is a cross-over design so analysis would be difficult without participants having crossed over to the opposite group.

7.3 Subject Population(s) for Analysis

Subject population for analysis will be any subject who is randomized, implanted with the device, and completed both halves of the crossover study.

8 Safety and Adverse Events

All adverse events occurring during the study, including those not meeting the criteria of an Unanticipated Adverse Device Effect (UADE) will be recorded on the appropriate case report form. Records of these events will be maintained and reports submitted to the FDA and IRB according to the regulatory requirements. Expected clinical adverse events and nonsignificant (not serious) clinical adverse events will not be reported. Expected clinical adverse events and anticipated adverse device effects are those listed in Section 1.5.2.

8.1 Definitions

Unanticipated Adverse Device Effect (UADE)
A UADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Adverse Effect (Event)

Any untoward medical occurrence in a subject involved in clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study related treatment(s).

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as an unanticipated adverse device effect unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization for diagnostic or elective procedures for a preexisting condition. Surgery will not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the local investigator should instruct each subject to report, to the local investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The local investigator should notify the study regulatory sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the local investigator should become aware of the development of problems, cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets all of the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new,

or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**

- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event Reporting Period

For this study, the study treatment follow-up period will end at the final visit (Visit 6). As this is approved therapy for chronotropic incompetence, no further monitoring for adverse events will be performed after the final visit.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Study subjects will be routinely questioned about adverse effects at study visits. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of the treatment group if applicable or suspected causal relationship to the investigational device or if applicable other study treatment or diagnostic product(s) will be recorded in the subjects' case history. For all adverse effects sufficient information will be pursued and or obtained as to permit; an adequate determination of the outcome, an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable other study treatment or diagnostic product. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome.

8.3 Sponsor-Investigator Reporting of Unanticipated Adverse Device Effects and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

The sponsor-investigator will promptly review documented Unanticipated Adverse Device Effects and as necessary shall report the results of such evaluation to FDA within **10** working days and Mayo IRB within **5** working days of initial notice of the effect. Thereafter the sponsor-investigator will submit such additional reports concerning the effect as requested.

8.3.1 Sponsor-Investigator Reporting, Notifying Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

8.3.2 Sponsor-Investigator Reporting: Notifying the FDA

The sponsor-investigator will report to the FDA all unanticipated adverse device effects according to the required reporting timelines, formats and regulations.

The sponsor-investigator will submit a completed FDA Form 3500A to the FDA's Center for Devices and Radiological Health for any observed or reported adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to the DSMB and all participating sub-investigators.

The completed FDA Form 3500A will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the sponsor-investigator first receives notice of the adverse effect.

If the results of the sponsor-investigator's follow-up evaluation shows that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the sponsor-investigator will submit a completed FDA Form 3500A as soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the sponsor-investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of any previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the sponsor-investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

Reporting Process
Unanticipated Adverse Device Effect reports will be submitted on FDA Form 3500A. The contact information for submitting reports is:

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Deviations from the investigational plan.

The sponsor-investigator shall notify Mayo IRB (see 21 CFR 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor-investigator is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB notification in accordance with 21 CFR 812.35(a) also is required.

8.4 Unblinding Procedures (Breaking the Blind) (as necessary if the study is blinded)

Every effort will be made to maintain blinding of patient and personnel in this study, except in the event of an emergency where it may become apparent which group the patient is in by witnessing pacer spikes on EKG or telemetry, or by needing to disable the pacer or change programming modes.

8.5 Stopping Rules

The study may be stopped if it becomes apparent that patients in the trial (in either group) are developing worsening heart failure symptoms, or needing hospitalization for heart failure which is reasonably felt by the investigators to be related to pacing, or the presence of the pacemaker or leads.

8.6 Medical Monitoring

It is the responsibility of the sponsor-investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see Section 10 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data comprise all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

An electronic system may be used as the primary means of recording clinical and laboratory data related to the study. Such a system will be compliant with the FDA electronic records and signatures regulations.

9.3 Case Report Forms

A Case Report Form (CRF) will be completed for each subject enrolled into the clinical study. The investigator-sponsor will review, approve and sign/date each completed CRF; the investigator-sponsor's signature serving as attestation of the investigator-sponsor's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

The study case report form (CRF) is the primary data collection instrument for the study and it may be an electronic form. All data requested on the CRF must be recorded. All missing

data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not obliterate, erase, or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management

Data will be managed electronically in a secure database to maintain patient data confidentiality and compliance with the Health Insurance Portability and Accountability Act (HIPAA).

Data Security and Confidentiality

Data will be encrypted and secured with individual logins and passwords for study personnel, with auditing and logging of changes and modification times.

Data Quality Assurance

Data will be verified at the time of entry into the database using a combination of double-entry, and computerized validation methods to ensure accuracy and reduce outliers or missing data.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for:

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Access to and Retention of Research Data Policy" [redacted] whichever is longer.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

This study will be monitored on a routine basis during the conduct of the trial. The Mayo Clinic Office of Research Regulatory Support will provide clinical monitoring for the trial as a service for the sponsor-investigator. Clinical trial monitoring requires review of the study data generated throughout the duration of the study to ensure the validity and integrity of the data along with the protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

10.2 Auditing and Inspecting

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the IRB, the monitor, and government regulatory agencies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The sponsor-investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as a sponsor-investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed and dated by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

This study is being financed primarily by research grants and sweep funds of the Mayo investigators. Secondary funding will be provided by Medtronic, Inc.

12.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

13 Publication Plan

Mayo and Investigators reserve the right to publish the result of work completed under this protocol. Prior review of the proposed publication by Medtronic will be provided, but in the interest of free exchange of scientific information, Mayo and Investigators may publish after the expiration of thirty (30) days following mailing of the proposed publication to Medtronic. Publication of the results will not include Confidential Information of Medtronic without the permission of Medtronic. In addition, Medtronic shall have the right to publish independently the results of the Study, provided, however, Mayo shall be the first to publish. In addition, any publication of data from the Study by Medtronic shall be considered a joint publication with Mayo as the co-author. After the publication of the primary paper, further ancillary studies using data collected in the trial may be analyzed and published by Mayo and Investigators.

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