Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	REVAMP Study (REmodeling the Left Ventricle with Atrial Modulated Pacing)
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Confidentiality Statement

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Jeff Lande, Prin. Statistician
2.0	• Updated CIP version to 3.0 • Updated signatories and roles • Grammatical and formatting updates, TOC, document date and version, removal of blue and unnecessary text (various sections) • Updated abbreviations (section 2) • Updated introduction with applicable abbreviations (section 3) • Updated subject enrollment numbers (now 50) and number of sites (now 10) (section 5.1) • Removed EQ-5D-5L from MNLWHF sections at 4 and 8 weeks (section 7.9.4) • Added 2 endpoints for EQ-5D-5L at 8 weeks (section 7.9.4) • Updated hypothesis for biomarkers to indicate biomarker assessment (section 7.9.7) • Updated changes to planned analyses to align with protocol V3.0 (section 7.10)	Kristie Wallace, Sr. Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADL	Activities of Daily Living
AE	Adverse Event
BPM	Beats per minutes
CH	Concentric Hypertrophic
CIP	Clinical Investigation Plan
CRF	Case Report Form
EF	Ejection Fraction
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
IDE	Investigational Device Exemption
LV	Left Ventricular/Ventricle
LVH	Left Ventricular Hypertrophy
LVEF	Left Ventricular Ejection Fraction
MMP	Matrix Metalloproteinase
MNLWHF	Minnesota Living With Heart Failure
NSR	Non-Significant Risk
NT-proBNP	N-terminal pro b-type Natriuretic Peptide
REVAMP	REmodeling the Left Ventricle with Atrial Modulated Pacing
SAP	Statistical Analysis Plan
SVT	Supraventricular Tachycardia
TIC	Tachycardia Induced Dilated Cardiomyopathy
TIMP	Tissue Inhibitor of Metalloproteinases
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
UR	Upper Rate

3. Introduction

An estimated 8.5 million people in the United States will have heart failure (HF) by 2030 (Heidenreich et al. 2013), and approximately 50% of these HF patients will have a preserved ejection fraction (HFpEF) (Owan et al. 2006). In contrast to HF with reduced EF (HFrEF), no effective drug or device therapies have been identified that improve the prognosis of the disease.

A large proportion of HFpEF patients have hypertension and have a concentric hypertrophic (CH) etiology described as an increased heart mass with increased relative wall thickness (Katz et al. 2013). Cardiomyocytes in HFpEF are thicker than HFrEF, and collagen content is increased compared to controls (Borlaug 2014). Patients with concentric hypertrophy or evidence of increased wall thickness are characterized by an increase in end diastolic pressures and isovolumic relaxation time (Liu et al. 1993) compared to normal controls. HFpEF patients have relatively normal volumes and EF, but they have a

reduced ability to adequately fill a stiffened left ventricle (LV). The impact of this diastolic dysfunction is more notable during exercise; HFpEF LVs are reliant on high left atrial pressures to fill the LV (Borlaug 2014). A search for a therapy that improves the compliance of the ventricle and improves early diastolic filling in these patients has not been successful.

We are proposing a pacing therapy that titrates a bolus of atrial pacing at 100 bpm delivered during sleeping hours with the hypothesis that raising heart rates can promote a beneficial LV dilation, which will reduce chamber stiffness and improve diastolic filling in HFpEF patients that have thickened ventricular walls and normal to small LV volumes. One challenge is finding a therapeutic heart rate dose that does not cause undesirable symptoms in ambulatory HF patients and a dose that achieves a desirable level of dilation to improve filling. Studies in animal models show that the dilatory effects of rapid pacing diminishes once the elevated pacing rates are discontinued (Tomita et al. 1991; Klein et al. 2016; Spinale et al. 1991); the study of dose response to elevated atrial pacing rate also includes monitoring the reaction of the heart to withdrawal of the pacing therapy.

Clinical studies of supraventricular tachycardia (SVT) rates and durations that cause LV dilation are limited. An extreme example of elevated heart rates promoting significant dilation and LV dysfunction comes from the clinical observation of SVT induced cardiomyopathy. Medi et al. (Medi et al. 2009) reported 10% incidence of tachycardia induced dilated cardiomyopathy (TIC) in N=345 patients undergoing ablation for atrial tachycardia. EF improved from 35 ± 11% to 59 ± 3% in the 2 months post-ablation. At the time of ablation treatment, the patients with LV dilation were characterized by slower ventricular response rates (117 ± 21 bpm vs 132 ± 33 bpm, p=0.05) and these patients reported that the duration of their symptoms started one or more years before seeking treatment. Conventional wisdom is that patients with more rapid ventricular responses are symptomatic and seek treatment more quickly before dilation and cardiomyopathy can occur from the rapid SVT.

Animal studies that have been used to study TIC have reported LV dilation and increased pulmonary capillary wedge pressures within 1 to 3 weeks when hearts are paced at extremely fast rates such as 240bpm (Tomita et al. 1991). However, the extent of dilation and symptoms can be titrated by choice of pacing rate and the duration of pacing. A study in a porcine model of concentric hypertrophy showed that 100% atrial pacing at 170bpm increased LV end-diastolic volumes by 246% in 4 weeks of pacing compared to an increase of 25% at a more modest rate of 125 bpm at 2 weeks of pacing (about 30bpm higher than normal sinus rhythm). The atrial pacing rate of 125bpm did not cause measurable changes in biomarkers including B-type natriuretic peptide (Klein et al. 2016).

Since this therapy is delivered in an ambulatory patient, the choice of pacing rate and duration to achieve a therapeutic dilation of the LV must not induce intolerable symptoms. A rate of 100bpm may be suitable for most HFpEF patients to respond favorably to stimulus rate, without symptoms. The nominal pacing rate setting for “Activities of Daily Living” (ADL) in Medtronic pacemakers is 95bpm and

the upper pacing rate (UR) is 130 bpm, so a sustained pacing rate of 100bpm is well within normal pacing range (Medtronic 2015). The acute hemodynamic response to elevated pacing rates in supine patients with CH has been characterized to have a blunted inotropic response to pacing rates above 100bpm compared to normal subjects (Liu et al. 1993). Stroke volumes have been shown to decrease from baseline as atrial pacing increases the rate above 120bpm in supine patients (Liu et al. 1993; Yamanaka et al. 2006; Westermann et al. 2008). The force-frequency effect was reported to be positive at rates 20 and 40bpm above intrinsic rates in patients with left ventricular hypertrophy (LVH) (Yamanaka et al. 2006). However, Inagaki et al (Inagaki et al. 1999) showed that the force frequency relationship can be biphasic in some patients with severe LVH, with a decrease in LV max +dp/dt observed in some patients as pacing rates increased above a range of 100-130bpm. At a structural level, HFpEF is typically associated with concentric remodeling with an increased left ventricular (LV) mass-to-volume ratio or overt LV hypertrophy and fibrosis. A high prevalence of this structural phenotype in HFpEF was recently confirmed in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial [22]. Despite the inclusion of patients with LV chamber dilation in this trial, about a quarter of patients had below-normal chamber volumes.

Pacing at an elevated rate for 100% of the day may accelerate changes in cardiac structure, but could be symptomatic if elevated rates sustained for long periods of time. Elevating heart rate for 5 hours during sleep at night may reduce the sensation to elevated rates and minimize symptoms for the patients. However, a heart rate dose of 5 hours will increase the overall duration required to promote dilation in the LV chamber. A measurable change in LV volumes was measured at 2 weeks of 100% pacing at 125bpm in animals (Klein et al. 2016), so a reasonable therapy duration of 100bpm for 5 hours per day would be 4 to 8 weeks of pacing before changes in LV volume would be measured. Measurement of biomarkers including matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) may be useful in understanding the time course of changes that lead changes in geometry. The matrix metalloproteinases (MMPs) are part of an enzymatic system that contribute to the remodeling of the extracellular matrix during rapid pacing-induced cardiomyopathy (Spinale et al. 1998). MMP-1, MMP-2, and MMP-3 were shown to increase in abundance at 7 days following initiation of rapid pacing, and were temporally related to a measured decrease in the collagen content as well as a lengthening of cardiomyocytes. TIMPs are also involved in inhibiting MMPs enzymatic activity and elevated TIMP-1 with reduction in MMPs were reported in HFpEF patients with LV hypertrophy (Ahmed et al. 2006).

This proposed elevated atrial rate pacing therapy is aimed at improving exercise capacity in HFpEF patients. In order to safeguard patients, we propose measuring blood biomarkers including troponin and NT-proBNP in order to monitor indications that the therapy is not causing ischemia or worsening heart failure. Natriuretic peptide release occurs in response to myocardial stretch. BNP and NT-proBNP are moderately elevated in HFpEF patients and may drop to normal levels in symptom-free periods (Meijers, van der Velde, and de Boer 2016). The European Society of Cardiology guidelines propose a cut-off of >35 pg/ml for BNP and >125 pg/ml for NT-proBNP to identify chronic, stable HFpEF patients

(Ponikowski et al. 2016). Thresholds for acute HF have been reported as 100pg/ml for BNP and 300 pg/ml for NT-proBNP, which give sensitivity of 0.95 and 0.99 respectively, and negative predictive value of 0.94 and 0.98, respectively (Roberts et al. 2015). In a study of patients hospitalized for acute decompensated heart failure, a positive Troponin test for myocardial infarction was defined using a threshold of 1.0 g/L or higher for cardiac Troponin I or 0.1 g/L for cardiac Troponin T (Turer et al. 2011). In an ambulatory chronic HFpEF population in 157 patients, the median value for Troponin I was 14 pg/mL (0.014 g/L) (Meijers et al. 2016). A Troponin T threshold of 0.02 ng/mL (0.02 g/L) was used in ambulatory HFpEF patients to detect myocardial injury; patients that had elevated Troponin T had an 78% rate of death or hospitalization at 18 months compared to 13% (Macin et al. 2006).

Metrics that will be used to evaluate whether there is a measurable therapeutic effect of the elevated atrial pacing rate therapy include serial measurements of quality of life, 6 Minute Walk Test, device-measured activity, echo measurements of volumes and diastolic function, and chronic changes in resting heart rate.

4. Study Objectives

4.1. Primary Objectives

The primary objective of this study is to assess the feasibility of using elevated night pacing as a therapy for HFpEF patients.

4.2. Ancillary/Exploratory Objectives

Adverse events, Minnesota Living With Heart Failure (MNLWHF) Questionnaire responses, EQ-5D-5L Questionnaire responses, 6 Minute Walk Test distances, resting heart rate, atrial fibrillation incidence, device-measured activity levels, echo measurements and blood samples will be collected at Baseline and follow-up visits. Adverse events will be collected and will be characterized to assess the overall safety and tolerability of the therapy. Changes in NT-proBNP and troponin concentrations from Baseline will also be used to assess patient safety. Early study patient withdrawals over the course of the study will be used to further assess therapy tolerability. Changes in quality of life, as assessed by the MN Living With Heart Failure and EQ-5D-5L, changes in 6 Minute Walk Test distance and change in activity levels will be compared from baseline to the various follow up time points to assess for therapy efficacy. Echo measurements and, optionally, peripheral blood concentrations of extracellular matrix biomarkers will be characterized and changes will be correlated with changes in the safety and efficacy assessments. End diastolic volume and mitral deceleration time could increase if the therapy works as hypothesized. If the quality of life, changes in 6 Minute Walk Test distance and/or activity levels improve, it will be of interest to see if the end diastolic volume and mitral deceleration time correlate with improvements. If the therapy works as hypothesized, other echo measurements, including left ventricular ejection

fraction (LVEF), might also change over time, although the direction and magnitude of these effects are difficult to predict. Characterizing these effects will be an important goal of the feasibility study.

As part of the exploratory/ancillary safety, tolerability and efficacy effects described in the REVAMP CIP, it will be of interest to characterize changes in collected measurements from Baseline to 4 weeks, compare changes in collected measurements at 4 weeks to 8 weeks in the subjects randomized to the elevated night pacing ON arm to subjects randomized to the elevated night pacing OFF arm and compare changes in collected measurements at 12 weeks to Baseline, 4 and 8 weeks to see whether any therapeutic improvements are sustained after the therapy is discontinued. If there are any nominally significant therapeutic effects at 4 or 8 weeks, those effects will specifically be explored further. Any effects that are significantly improved at 4 weeks compared to baseline will be explored at 8 and 12 weeks compared to baseline to determine if these effects are sustained. Similarly, any effects that are nominally significant between subjects on and off therapy between 4 and 8 weeks will be explored at 12 weeks to determine if improvements are sustained.

5. Investigation Plan

5.1. Study Design

The REVAMP Clinical Study will be a multi-center, prospective, randomized, single-blinded, clinical feasibility study. Subjects will be randomized in a 2:1 ratio to elevated night pacing ON or elevated night pacing OFF.

It is expected that up to 50 subjects may be enrolled to ensure 30 subjects undergo elevated night pacing at approximately 10 sites in the United States to ensure enrollment completion within the pre-specified timeframe.

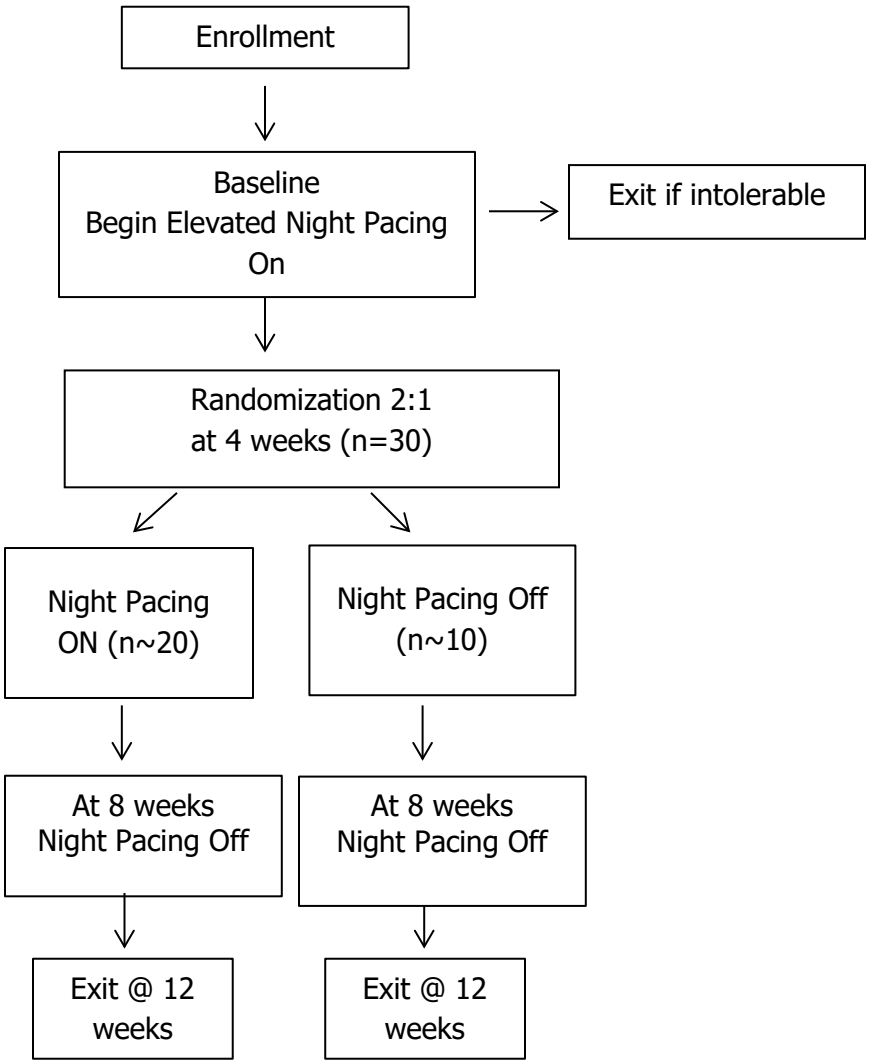
The REVAMP study will be conducted as a Non-Significant Risk (NSR) IDE study. The REVAMP Research System does not include an investigational device; the ability to program a lower rate of 100 bpm is available in market-released pacemakers, and the Sleep function (which allows a different rate to be programmed for part of a 24-hour clock) is an approved feature in market-released pacemakers that will be used in the clinical study. The study will be conducted in compliance with 21 CFR Parts 11, 50, 56, 812.2(b)(1). This study does not require an IDE submission to FDA.

The Sleep Function will be programmed so that the pacemaker can deliver an elevated pacing rate of 100 bpm during the night for 5 hours and lower the rate during the daytime hours. This is within the FDA-approved programmable parameters of the Sleep Function feature.

The study will collect the following information: demographics, medical history, medications, standard physical, NYHA class, blood samples to measure NT-proBNP, Troponin and other biomarkers, echo

measurements, MN Living with Heart Failure Questionnaire, EQ-5D-5L Questionnaire, 6 Minute Walk Test, implanted device information, device interrogations, save-to-media, adverse events (including death), system modifications, and exit information. The MN Living with Heart Failure Questionnaire was chosen to measure the quality of life for subjects with heart failure, which includes a question on how well the subject is sleeping at night.

Figure 1: In Office Study Visits



5.2. Study Population

This study will enroll patients who have a Medtronic dual chamber pacemaker system with the Sleep function per local guidelines and who meet all of the specific study inclusion criteria and none of the exclusion criteria.

All subjects in this investigation have received a Medtronic dual chamber pacemaker for approved indications. HFpEF subjects who have a small to normal LV volume and evidence of LV hypertrophy and/or increased LV wall thickness will be selected for this study.

5.3. Study Procedures

Clinical data is collected at designated time points throughout the study as indicated in Table 1 below. Data will be collected using eCRFs, an electronic data management system for clinical studies. At the baseline, 4 week, 8 week, and 12 week visits subjects are to fill out the MN Living with Heart Failure Questionnaire and perform a 6 Minute Walk Test. At the same visits, an echocardiogram must be done, for which instructions are provided in an Echocardiography Handbook (provided under separate cover). A blood draw must also be done, (instructions are provided under separate cover.) The device programming should occur after all other study procedures are complete, except for the final device interrogation and save-to-media. The EQ-5D-5L Questionnaire will only be collected at the Baseline and 8 week visits.

In addition to eCRF data, non-eCRF data will be collected to include device interrogation files/save-to-media and digital echo data.

Table 1: Study Procedures

Study Procedure	Enroll-ment	Baseline	Telephone Call Follow Up Visits (24 Hour, 5 days, 2 weeks, 6 weeks, 10 weeks)	4 week visit	8 week visit	12 week visit (Study Exit)	Early Study Exit	Unscheduled Visit
Informed consent	x							
Inclusion/exclusion	x	x						
Demographics		x						
Medical History		x						
Medications		x	X	x	x	x	X	x**

Study Procedure	Enroll-ment	Baseline	Telephone Call Follow Up Visits (24 Hour, 5 days, 2 weeks, 6 weeks, 10 weeks)	4 week visit	8 week visit	12 week visit (Study Exit)	Early Study Exit	Unscheduled Visit
Physical Assessment		x		x	x	x		x**
NYHA class		x		x	x	x		
MN Living with Heart Failure Questionnaire		x		x	x	x		
EQ-5D-5L Questionnaire		x			x			
6 Minute Walk Test		x		x	x	x		
Echo		x		x	x	x		x**
Blood Draw		x		x	x	x		x**
Initial Device Interrogation/Save-to-media		x		x	x	x	x	x**
Device Programming		x		x*	x*		x**	x**
Final Device Interrogation/ Save-to-Media		x		x	x	x	x	x**
At least 30 minute observation period post device programming		x						
Symptom Assessment			X	x	x	x		x**
Heart Rate (using finger oximeter)			X					
Crossover			As they occur					
System modifications	As they occur							

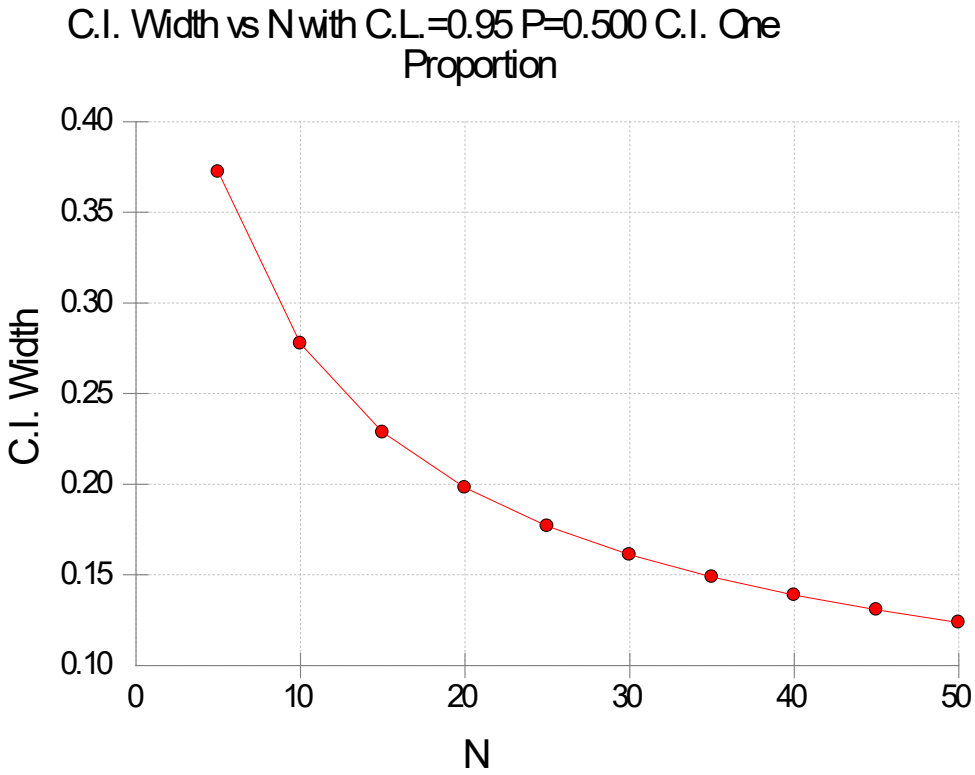
Study Procedure	Enroll-ment	Baseline	Telephone Call Follow Up Visits (24 Hour, 5 days, 2 weeks, 6 weeks, 10 weeks)	4 week visit	8 week visit	12 week visit (Study Exit)	Early Study Exit	Unscheduled Visit
Adverse events (AEs)/Death	As they occur							
Device Deficiencies	As they occur							
Study deviations	As they occur							
Study Exits	As they occur							

* See programming recommendations for the follow up visit
** If deemed necessary by the investigator

6. Determination of Sample Size

As a feasibility study, this study is not powered to meet any specific endpoints. While this feasibility study is not powered to formally test a hypothesis, it is expected that a sample of up to 30 subjects will be sufficient to determine whether this approach warrants further study. The 4 week safety and tolerability objective described in Section 7.9.1 will help determine whether to move forward with this therapy. Figure 2 indicates that improvements in the confidence interval width at various proportions of subjects meeting the 4 week safety and tolerability endpoint beyond 30 subjects are relatively small.

Figure 2: 95% Confidence Interval Widths for Various Proportions of 4 Week Safety and Tolerability Endpoint


C.I. Width vs N with C.L.=0.95 P=0.500 C.I. One Proportion
C.I. Width
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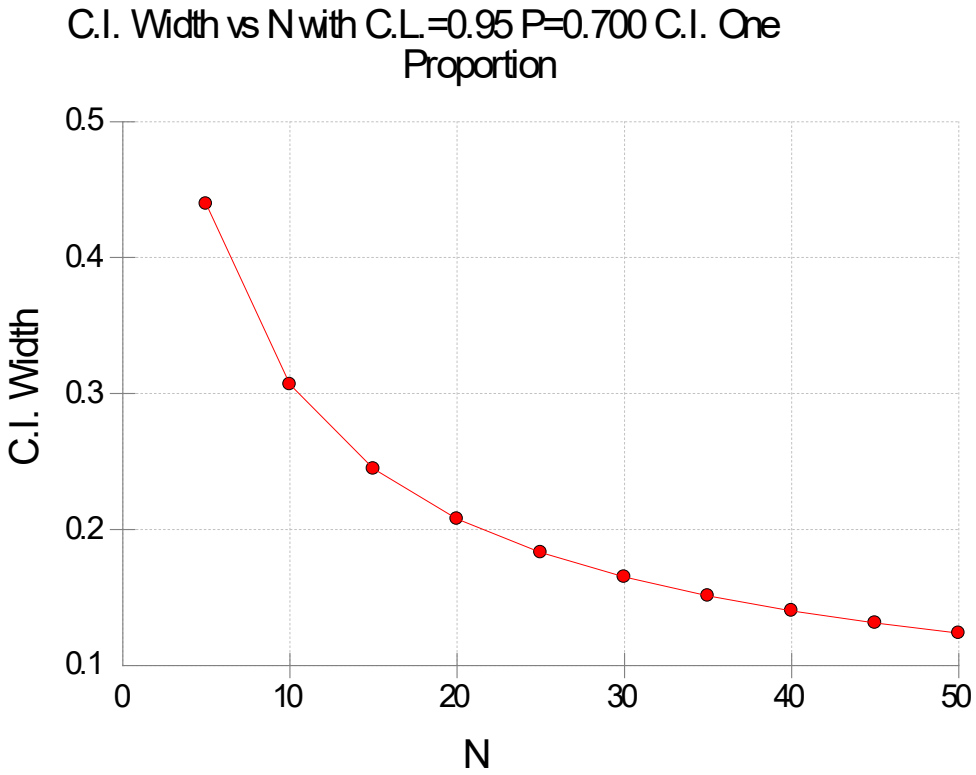
0.35
0.30
0.25
0.20
0.15
0.10
0
10
20
30
40
50
N


C.I. Width vs N with C.L.=0.95 P=0.700 C.I. One Proportion
C.I. Width
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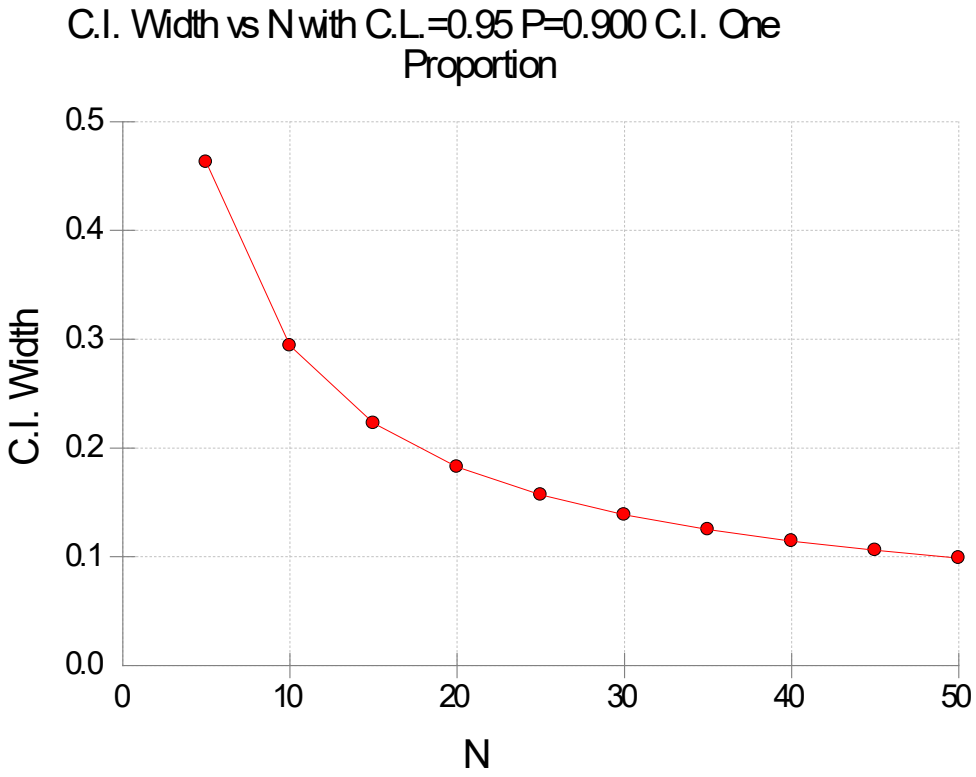
0.4
0.3
0.2
0.1
0
10
20
30
40
50
N



7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Subject disposition will be summarized by a CONSORT flow diagram, based on the subject flow diagram shown in Figure 1, but providing additional details on subject attrition.

7.1.2. Clinical Investigation Plan (CIP) Deviations

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness, blood sample or echo lost at Core Lab).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary endpoint analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported to Medtronic regardless of whether they are medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation must be recorded in Oracle Clinical. Refer to the CIP for an explanation for the deviations.

In the event the deviation involves a failure to obtain a subject's informed consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB as well as Medtronic as soon as possible but no later than five (5) working days, or according to local requirements. Reporting of all other study deviations should comply with the IRB policies and/or local laws and deviations must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the Clinical Investigation Plan, conduct additional training, terminate the study). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic may provide site-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

7.1.3. Analysis Sets

A set of analysis datasets will be created based on case report forms (enrollment, baseline, randomization). Flagging variables will indicate whether a subject passed various study milestones, such as whether the subject could tolerate the study therapy at baseline visit testing and initiated the study therapy.

7.2. General Methodology

Medtronic employees or designees will perform all statistical analyses. Additional exploratory analyses of the data may be conducted as deemed appropriate. Data analysis may be carried out throughout the study without having all enrolled subjects completing study required follow-ups.

7.3. Center Pooling

Centers/investigators will be pooled for analysis of study objectives.

7.4. Handling of Missing, Unused, and Spurious Data and Dropouts

Missing data imputation methods will not be used for the study objectives unless specified otherwise within the analysis methods.

7.5. Adjustments for Multiple Comparisons

No adjustments are planned for multiple comparisons.

7.6. Demographic and Other Baseline Characteristics

Baseline characteristics and relevant medical history will be collected on eCRFs for all enrolled subjects. Baseline characteristics will be summarized for all enrolled subjects. Baseline variables to be summarized may include, but are not limited to: age, sex, race, height, weight, NYHA, medical history (symptoms) and general cardiovascular history. Baseline blood and echo measurements will be summarized from data sets prepared by the blood and echo core labs, respectively.

For continuous variables, mean, standard deviation, median, and range will be reported. For categorical variables, frequency and percentage will be reported.

7.7. Treatment Characteristics

After enrollment in the REVAMP clinical study, at each protocol required follow-up, the investigator must evaluate the subject's health, assess for any adverse events or medication changes, and interrogate the study device to verify appropriate study device function.

7.8. Interim Analyses

Abstracts, posters and presentations could be generated on this dataset throughout the study. No type I error correction or alpha spending will be performed for analyses conducted in support of deliverables occurring while the study is ongoing.

7.9. Evaluation of Objectives

7.9.1. Ancillary Safety and Tolerability Endpoint

Safety and Tolerability – 4 weeks

Hypothesis

A 4 week period of elevated night pacing is safe and tolerable.

Analysis Methods

The proportion of subjects who remain in the study up until the 4 week visit without exiting due to intolerable symptoms, increase in NT-proBNP levels, decrease in LVEF or increase in troponin will be calculated along with the lower bound of the one-sided 95% confidence interval.

As the REVAMP study was designed to explore the feasibility of the study therapy, there was no pre-specified threshold for overall safety and tolerability. In order to provide the most conservative estimate of the safety and tolerability, any study exit prior to the 4 week visit will be assumed to be related to intolerable symptoms or safety issue. Also, study

deaths attributed by the investigative site as related or unknown relative to the study therapy prior to the 4 week visit will be counted against the proportion of subjects remaining in the study. A variable active4wk will be set to equal 1 for subjects who remain in the study up until the 4 week visit and will be set to equal 0 otherwise. The proportion of subjects remaining in the study, along with the lower bound of the one-sided 95% confidence interval can be found using code similar to:

```
PROC FREQ DATA=Revamp_Test;
   TABLE active4wk / BINOMIAL(EXACT LEVEL='1') ALPHA=0.1;
RUN;
```

As this study is exploring the feasibility of the study therapy, sensitivity analysis may be performed, exploring various assumptions regarding ambiguous study exits.

Determination of Subjects for Analysis

All enrolled subjects that are programmed with elevated night pacing.

Safety and Tolerability – 8 weeks

Hypothesis

Following a 4 week period of elevated night pacing, compare the safety and tolerability of subjects in the ON and OFF arm for an additional 4 weeks of elevated night pacing

Analysis Methods

The proportion of subjects who remain in the study from the 4 week visit to the 8 week visit without exiting due to intolerable symptoms, increase in NT-proBNP levels, decrease in LVEF or increase in troponin will be calculated along with the lower bound of the one-sided 95% confidence interval for both arms (elevated night pacing left ON versus elevated night pacing programmed OFF).

This analysis will be similar to the 4 week safety and tolerability endpoint, using a variable active8wk to indicate whether a subject remains in the study up until the 8 week visit. The same conservative approach to study exits and death used for the 4 week time point will be implemented for the 8 week time point. The proportion of subjects remaining in the study,

along with the lower bound of the one-sided 95% confidence interval can be found using code similar to:

```
PROC FREQ;
   TABLE active8wk / BINOMIAL(EXACT LEVEL='1') ALPHA=0.1;
RUN
```

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this analysis.

7.9.2. Ancillary Safety Endpoint – NT-proBNP, troponin, LVEF

NT-proBNP, troponin, LVEF – 4 weeks

Hypothesis

For each of the main safety measures (NT-proBNP, troponin and LVEF), comparisons will be done to see if there are changes from baseline after a 4 week period of elevated night pacing.

Analysis Methods

A paired comparison of the value at the end of the period compared to the value at the start of the period will be calculated. A two-sided paired t-test will be performed testing the hypothesis

H_o: $\mu = 0$

H_a: $\mu \neq 0$

Where μ = difference in measurement from baseline to week 4 visit

SAS code similar to the following will be used to evaluate the 4 week ancillary safety endpoints:

```
PROC TTEST;
   PAIRED ntprobnp0*ntprobnp4;
RUN;

PROC TTEST;
```

```
   PAIRED troponin0*troponin4;
RUN;

PROC TTEST;
   PAIRED lvef0*lvef4;
RUN;
```

By default, subjects that do not have 4 week measurements available will be excluded from the analysis.

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis.

NT-proBNP, troponin, LVEF – 8 weeks

Hypothesis

For each of the main safety measures (NT-proBNP, troponin and LVEF), it will be assessed whether there is a difference in the change of the measurement following an additional 4 week period of elevated night pacing after an initial 4 week period of elevated night pacing compared to that period of 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing.

Analysis Methods

A paired comparison of the measurement at the 8 week visit compared to the measurement at the 4 week visit period compared to the value at the start of the period will be calculated. A two-sided paired t-test will be performed testing the hypothesis

H_o: $\mu_{ON} = \mu_{OFF}$

H_a: $\mu_{ON} \neq \mu_{OFF}$

Where μ_{ON} = difference in NT-proBNP, troponin or LVEF from week 4 to week 8 for subjects in the ON arm and μ_{OFF} = difference in those measurements in subjects in the OFF arm

SAS code similar to the following will be used to evaluate the 8 week ancillary safety endpoints, where the variables in the VAR statement will equal the difference between the 8 week and 4 week measurements:

```
PROC TTEST;
   CLASS trt;
   VAR ntprobnpdiff;
RUN;

PROC TTEST;
   CLASS trt;
   VAR troponindiff;
RUN;

PROC TTEST;
   CLASS trt;
   VAR lvefdiff;
RUN;
```

An ANCOVA model may also be used for all analyses prospectively planned as T-tests, in addition to the T-tests for this and other similar ancillary objectives comparing the 4 and 8 week data by randomized treatment group. ANCOVA models may be implemented using SAS code similar to

```
PROC GLM;
   CLASS trt;
   MODEL ntprobnpdiff= trt ntprobnp0;
   LSMEANS trt / pdiff cl alpha=0.05;;
RUN;
```

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. NT-proBNP, troponin or LVEF at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8.

7.9.3. Ancillary Safety Endpoint – Adverse Events

Adverse Events – 4 weeks

Hypothesis

Not applicable. This endpoint is to characterize adverse events during the first 4 weeks of elevated night pacing.

Analysis Methods

Summarization of adverse events by MedDRA preferred term. Summarization may include pertinent subgroups, including all potentially related events and all CV-related events.

Determination of Subjects for Analysis

All adverse events reported for subjects actively receiving elevated night pacing will be included.

Adverse Events – 8 weeks

Hypothesis

There are differential rates of adverse event reporting between subjects randomized to receive elevated night pacing and subjects randomized to elevated night pacing OFF. In addition, adverse events for subjects continuing to receive elevated night pacing will be characterized and extended from the AE's collected during the first 4 weeks.

Analysis Methods

The adverse event reporting rate during the period from week 4 to week 8 in subjects in the ON arm and OFF arm will be compared and characterized.

The Mean Cumulative Function will be used to compare the adverse event reporting rate between the ON arm and the OFF arm. This analysis will be in the framework of the Andersen-Gill mode, which is a generalization of Cox's proportional hazard model, comparing the distribution of events between groups and accounts for multiple events within a subject. To execute this analysis, a data set will need to be derived from the data set of all adverse events that occurred in randomized subjects ordered by subject, using SAS code similar to

```
PROC SQL NOPRINT;
   CREATE TABLE Adverse_MCF_Setup AS SELECT pt, trt, randomdt,
        exitdate, aestdt
   FROM A_Adverse
   WHERE ^MISSING(randomdt)
   ORDER BY pt, aestdt;
QUIT;
```

The variables TStart and TStop will be coded as 0 or 1, with the initial value of TStart for each subject equal to the 0, representing the randomization date. TStop will be the number of days until either an event or censor. Each subsequent TStart will be the previous TStop value in days and the corresponding TStop date will be the sum of the value of TStart and the number of days until the next event or censor. That data set will be constructed using SAS code similar to

```
DATA Adverse_MCF;
   SET Adverse_MCF_Setup;
   BY pt aestdt;
   RETAIN prev_stop;
   IF first.pt THEN DO;
         Tstart=0;
/*       No adverse events - first record*/
         IF MISSING(aestdt) THEN DO;
               Tstop=exitdate-randomdt;
               status=0;
         END;
         ELSE DO;
               Tstop=aestdt-randomdt;
               status=1;
               prev_stop=Tstop;
         END;
         OUTPUT;
   END;
   ELSE IF ^MISSING(aestdt) THEN DO;
         Tstart=prev_stop;
         Tstop=aestdt-randomdt;
         status=1;
         prev_stop=Tstop;
         OUTPUT;
         IF last.pt THEN DO;
               Tstart=aestdt-randomdt;
               Tstop=exitdate-randomdt;
               status=0;
               OUTPUT;
         END;
   END;
RUN;
```

A data set with a single variable trt with two rows with values 0 and 1 (representing the control and treatment arm) will be created and the analysis will then be implemented using SAS code similar to

```
PROC PHREG DATA=Adverse_MCF COVS(aggregate) covm PLOTS(overlay)=MCF;
   MODEL (Tstart, Tstop)*status(0)=trt;
   BASELINE covariates=IN2 out=OUT2 cmf=_all_ / NOMEAN;
```

```
   ID pt;
RUN;
```

Determination of Subjects for Analysis

Rates of adverse events for subjects randomized to OFF will be calculated over the full period of follow-up, while rates of adverse events for subjects randomized to ON will be calculated only during the period that subjects were actually receiving elevated night pacing.

7.9.4. Ancillary Efficacy Endpoint - Quality of Life

MNLWHF Questionnaire – 4 weeks

Hypothesis

There is an improvement in quality of life of an additional 4 week period of elevated night pacing after an initial 4 week period of elevated night pacing compared to that period of 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing, as assessed by the MNLWHF questionnaire.

Analysis Methods

A paired comparison of the value at the end of the period compared to the value at the start of the period will be calculated. A one-sided paired t-test will be performed testing the hypothesis

$H_o: \mu \leq 0$

$H_a: \mu > 0$

Where μ = difference in quality of life score from baseline to week 4 visit

Quality of life is assessed via the MNLWHF questionnaire by the sum of the response values of the 21 questions. If not all, but at least 17 of the questions on the questionnaire are completed, the score will be summed and normalized to a scale of 0-105, based on the number of questions answered.

SAS code similar to the following will be used to evaluate the 4 week MNLWHF endpoint:

```
PROC TTEST;
   PAIRED mnlwhf0*mnlwhf4;
RUN;
```

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis. MNLWHF questionnaire responses will only be included if at least 17 of the 21 questions are completed at baseline and 4 weeks.

MNLWHF Questionnaire – 8 weeks

Hypothesis

There is an improvement in quality of life of an additional 4 week period of elevated night pacing after an initial 4 week period of elevated night pacing compared to that period of 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing, as assessed by the MNLWHF questionnaire.

Analysis Methods

A paired comparison of the scores at the 8 week visit compared to the score at the 4 week visit period compared to the value at the start of the period will be calculated. A one-sided paired t-test will be performed testing the hypothesis

$H_o: \mu_{ON} \leq \mu_{OFF}$

$H_a: \mu_{ON} > \mu_{OFF}$

Where μ_{ON} = difference in quality of life score from week 4 to week 8

SAS code similar to the following will be used to evaluate the effect of the study therapy on the MNLWHF endpoint between week 4 and week 8:

```
PROC TTEST;
   CLASS trt;
   VAR mnlwhfdiff;
RUN;
```

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. MNLWHF scores at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the

study from week 4 to week 8. MNLWHF questionnaire responses will only be included if at least 17 of the 21 questions are completed at both 4 and 8 weeks.

EQ-5D-5L Questionnaire – 8 weeks

Hypothesis

There is an improvement in quality of life from baseline after an 8 week period of elevated night pacing, as assessed by the EQ-5D-5L Questionnaire. This assumes the effect is the same whether or not elevated night packing is turned off at week 4.

Analysis Methods

A paired comparison of the value at the end of the period compared to the value at the start of the period will be calculated. A one-sided paired t-test will be performed testing the hypothesis

H_o: $\mu \leq 0$

H_a: $\mu > 0$

Where μ = difference in EQ-5D-5L score from baseline to week 8 visit

The EQ-5D-5L summary health score is calculated based on five "dimension" questions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each dimension has five options which are: 1=no problem, 2=slight problem, 3=moderate problem, 4=severe problem, 5=unable to perform.

SAS code similar to the following will be used to evaluate the 8 week EQ-5D-5L endpoint:

```
PROC TTEST;
   PAIRED eq5d0*eq5d8;
RUN;
```

Determination of Subjects for Analysis

All subjects that completed 8 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis. EQ-5D-5L questionnaire responses will only be included if all 5 questions were answered at baseline and 8 weeks. EQ-5D-5L score at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8.

Hypothesis

There is more of an improvement in quality of life after an 8 week period of elevated night pacing than for a 4 week period of elevated night pacing followed by 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing, as assessed by the EQ-5D-5L questionnaire.

Analysis Methods

A paired comparison of the scores at the 8 week visit compared to the score at the baseline visit will be calculated. A one-sided paired t-test will be performed testing the hypothesis

H_o: $\mu_{ON} \leq \mu_{OFF}$

H_a: $\mu_{ON} > \mu_{OFF}$

Where μ_{ON} = difference in EQ-5D-5L score from baseline to week 8

SAS code similar to the following will be used to evaluate the effect of the study therapy on the EQ-5D-5L endpoint between baseline and week 8:

```
PROC TTEST;
   CLASS trt;
   VAR eq5ddiff;
RUN;
```

Determination of Subjects for Analysis

All subjects that completed 8 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis. EQ-5D-5L scores at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8. EQ-5D-5L questionnaire responses will only be included if all 5 questions were answered at baseline and 8 weeks.

7.9.5. Ancillary Efficacy Endpoint: Mobility and Activity

6 Minute Walk Test Distance – 4 weeks

Hypothesis

There is an improvement in the 6 Minute Walk Test distance from baseline after a 4 week period of elevated night pacing.

Analysis Methods

A paired comparison of the value at the end of the period compared to the value at the start of the period will be calculated. A one-sided paired t-test will be performed testing the hypothesis

H_o: $\mu \leq 0$

H_a: $\mu > 0$

Where μ = difference in 6 Minute Walk Test distance from baseline to week 4 visit

SAS code similar to the following will be used to evaluate the 4 week 6 Minute Walk Test endpoint:

```
PROC TTEST;
   PAIRED sixminwalk0*sixminwalk4;
RUN;
```

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis. Subjects that did not take the 6 Minute Walk Test at either baseline or week 4 will be assigned a distance of 0 for the missed visit. A sensitivity analysis may be done excluding subjects instead of assigning a distance of 0.

6 Minute Walk Test Distance – 8 weeks

Hypothesis

There is an improvement in the 6 Minute Walk Test distance from an additional 4 week period of elevated night pacing after an initial 4 week period of elevated night pacing

compared to that period of 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing.

Analysis Methods

A paired comparison of the scores at the 8 week visit compared to the score at the 4 week visit period compared to the value at the start of the period will be calculated. A one-sided paired t-test will be performed testing the hypothesis

H_o: $\mu_{ON} \leq \mu_{OFF}$

H_a: $\mu_{ON} > \mu_{OFF}$

Where μ_{ON} = difference in 6 Minute Hall Walk distance from week 4 to week 8 in subjects randomized to the ON arm and μ_{OFF} = difference in 6 Minute Hall Walk distance from week 4 to week 8 in subjects randomized to the OFF arm.

SAS code similar to the following will be used to evaluate the effect of the study therapy on the 6 Minute Hall Walk endpoint between week 4 and week 8:

```
PROC TTEST;
   CLASS trt;
   VAR sixminwalkdiff;
RUN;
```

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. 6 Minute Walk Test distance at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8. Subjects that did not take the 6 Minute Walk Test at either week 4 or 8 will be assigned a distance of 0 for the missed visit. A sensitivity analysis may be done excluding subjects instead of assigning a distance of 0.

Device-measured activity levels – 4 weeks

Hypothesis

There is an improvement in daytime activity levels from baseline over a 4 week period of elevated night pacing.

Analysis Methods

Activity levels over time will be characterized over time from baseline to the 4 week visit. Daily activity level is recorded by the Cardiac Compass feature in most devices. Since subjects enrolled in the study have had their pacemaker for at least 6 month, they will have activity levels prior to enrollment in the study. The daily activity levels in the 2 weeks prior to the date of therapy initiation (period 1) will be compared to daily activity levels around the 4 week visit. Specifically, the activity level on the date of the 4 week visit and the 3 days prior to and subsequent to that date will comprise the week 4 comparison group (period 2). Those periods will be retrieved from the Cardiac Compass activity level data using SAS code similar to the following, where the Activity_Baseline data set contains all of the Cardiac Compass dates (entryday), along with the date of therapy initiation (therapydt) on each record.

```
DATA Activity_Week4;
   SET Activity_Baseline;
   IF -8 < entryday-therapydt < 0 THEN DO;
         period = 1;
         OUTPUT;
   END;
   IF -15 < entryday- therapydt LE -8 THEN DO;
         period=1;
         OUTPUT;
   END;
/*       Straddle the week 4 date - the 4 week date and the 3 days
before and after the 4 week date */
   IF (w4date-3) LE entryday- therapydt LE (w4date+3) THEN DO;
         period=2;
         OUTPUT;
   END;
RUN;
```

The analysis will be performed using linear mixed effects modeling, using SAS code similar to

```
PROC MIXED DATA=Activity_Week;
   CLASS pt period;
   MODEL activityperday = period;
   RANDOM pt;
   LSMEANS period / PDIFF=all alpha=0.05;
RUN;
```

Additional analyses, using similar methodology, may be done to explore other potential effects of therapy, including whether there is an immediate impact on activity following therapy initiation.

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis.

Device-measured activity levels – 8 weeks

Hypothesis

There is an improvement in daytime activity levels over an additional 4 week period of elevated night pacing after an initial 4 week period of elevated night pacing compared to that period of 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing.

Analysis Methods

Activity levels over time will be characterized over time from the 4 week visit to the 8 week visit and compared between the subjects with the elevated pacing programmed ON versus OFF. Analysis will be similar to the 4 week activity level endpoint. The date of the 8 week visit and the 3 days prior to and subsequent to it will comprise the 8 week window.

Those periods will be retrieved from the Cardiac Compass activity level data using SAS code similar to the following

```
DATA Activity_Week8;
   SET Activity_Consent;

/*      Straddle the week 4 date - the 4 week date and the 3 days
before and after the 4 week date */
   IF (w4date-3) LE entryday-consdt LE (w4date+3) THEN DO;
         period=1;
         OUTPUT;
   END;

/*      Straddle the week 8 date - the 8 week date and the 3 days
before and after the 8 week date */
   IF (w8date-3) LE entryday-consdt LE (w8date+3) THEN DO;
         period=2;
         OUTPUT;
   END;

RUN;
```

The analysis will be performed using linear mixed effects modeling, using SAS code similar to

```
PROC MIXED DATA=Activity_Week8;
   CLASS pt period trt;
   MODEL activityperday = period trt period*trt;
   RANDOM pt;
   LSMEANS period trt period*trt / PDIFF=all ALPHA=0.05;
RUN;
```

A significant p-value for the interaction between period and treatment would suggest that there is incremental value in continuing high rate pacing from week 4 to week 8.

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Daytime activity levels up to time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8.

7.9.6. Ancillary Efficacy Endpoint – Echo Measurements

Echo measurements – 4 weeks

Hypothesis

All echo measurements will be assessed to see if there are changes from baseline after a 4 week period of elevated night pacing.

Analysis Methods

A paired comparison of the value at the end of the period compared to the value at the start of the period will be calculated. A two-sided paired t-test will be performed testing the hypothesis

H_o: $\mu = 0$

H_a: $\mu \neq 0$

Where μ = difference in measurement from baseline to week 4 visit

SAS code similar to the following will be used to evaluate any echo measurement assessed as a continuous variable:

```
PROC TTEST;
```

```
   PAIRED echotestn_0* echotestn_4;
RUN;
```

If any of the echo measurements of interest are collected as categorical variables with binary outcomes, the data will be reshaped to a vertical data file with columns for subject id, echo test value (0 or 1) and time, which will be 0 for the baseline echo and 4 for the 4 week echo, unless the subject exited the study early, in which time will be calculated as the time elapsed from baseline to exit. Then, a general linear mixed model will test whether there was an improvement in the echo test over time, using SAS code similar to:

```
PROC GLIMMIX;
   CLASS pt time;
   MODEL echotest = time / dist=binary link=logit;
   RANDOM intercept / subject=pt;
RUN;
```

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis.

Echo measurements – 8 weeks

Hypothesis

All echo measurements will be assessed to determine whether there is a difference in the change of the measurement following an additional 4 week period of elevated night pacing after an initial 4 week period of elevated night pacing compared to that period of 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing.

Analysis Methods

A paired comparison of the measurement at the 8 week visit compared to the score at the 4 week visit period compared to the value at the start of the period will be calculated. A two-sided paired t-test will be performed testing the hypothesis

H_o: $\mu_{ON} = \mu_{OFF}$

H_a: $\mu_{ON} \neq \mu_{OFF}$

Where μ_{ON} = difference in echo measurement from week 4 to week 8 in subjects randomized to the ON arm and μ_{OFF} = difference in echo measurement from week 4 to week 8 in subjects randomized to the OFF arm

SAS code similar to the following will be used to evaluate the effect of the study therapy between week 4 and week 8 on echo measurement assessed as continuous variables:

```
PROC TTEST;
   CLASS trt;
   VAR echotestdiff;
RUN;
```

If any of the echo measurements of interest are collected as categorical variables with binary outcomes, the analysis will be done similar to the comparison between the 4 and 8 week measurements. An extra column, indicating the treatment arm will need to be included. The analysis will be performed using SAS code similar to

```
PROC GLIMMIX DATA=EchoTime2 METHOD=RMPL;
   CLASS pt time trt;
   MODEL echotest = time trt time*trt / dist=binomial link=logit;
   RANDOM intercept / subject=pt;
RUN;
```

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Echo measurement at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8.

7.9.7. Ancillary Efficacy Endpoint – Collagen Degradation Biomarker Measurements

Biomarker measurements – 4 weeks

Hypothesis

If the results of the safety, tolerability and efficacy of elevated night pacing appear to be promising, additional work may be done to assess collagen degradation biomarker measurements to see if there are changes from baseline after a 4 week period of elevated night pacing.

Analysis Methods

A paired comparison of the value at the end of the period compared to the value at the start of the period will be calculated. A two-sided paired t-test will be performed testing the hypothesis

H_o: $\mu = 0$

H_a: $\mu \neq 0$

Where μ = difference in measurement from baseline to week 4 visit

SAS code similar to the following will be used to evaluate the change in each relevant biomarker measurement:

```
PROC TTEST;
   PAIRED biomarkern_0* biomarkern_4;
RUN;
```

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Subjects that were unable to tolerate or withdrew from the treatment during the first 4 weeks because of safety or other issues will not be included in this efficacy analysis.

Biomarker measurements – 8 weeks

Hypothesis

If the results of the safety, tolerability and efficacy of elevated night pacing appear to be promising, additional work may be done to determine whether there is a difference in the change in the collagen degradation biomarker measurements following an additional 4 week period of elevated night pacing after an initial 4 week period of elevated night pacing compared to that period of 4 weeks with the elevated night pacing programmed OFF after the initial 4 weeks period of elevated night pacing.

Analysis Methods

A paired comparison of the measurement at the 8 week visit compared to the score at the 4 week visit period compared to the value at the start of the period will be calculated. A two-sided paired t-test will be performed testing the hypothesis

H_o: $\mu_{ON} = \mu_{OFF}$

H_a: $\mu_{ON} \neq \mu_{OFF}$

Where μ_{ON} = difference in collagen degradation biomarker measurement from week 4 to week 8 in subjects randomized to the ON arm and μ_{OFF} = difference in collagen degradation biomarker measurement from week 4 to week 8 in subjects randomized to the OFF arm

SAS code similar to the following will be used to evaluate the effect of the study therapy between week 4 and week 8 on each biomarker measurement:

```
PROC TTEST;
   CLASS trt;
   VAR biomarkerdiff;
RUN;
```

Determination of Subjects for Analysis

All subjects that completed 4 weeks of elevated night pacing. Biomarker measurement at time of exit will be used for subjects that do not complete the full 4 weeks of participation in the study from week 4 to week 8.

7.9.8. Ancillary Efficacy Endpoint – Sustained effects of elevated night pacing

Hypothesis

it will be explored whether there are sustained effects of elevated night pacing.

Analysis Methods

These analyses will be exploratory in nature, involving characterizing changes from baseline and end of therapy to the last follow-up visit. Generally speaking, all tests described above may be analyzed at week 12 compared to baseline, week 4 or week 8. Specific tests of interest will include

- For any measurement found significant at week 4
  - A test for subjects with high rate pacing set to OFF at week 4 will be done to compare the measurement at week 8 with both baseline and week 4

- A test for subjects for subjects with high rate pacing set to ON at week 4 will be done to compare the measurement at week 12 with baseline, week 4 and week 8

▪ For any measurement found significant by treatment at week 8

- A test for subjects with rate pacing set to ON at week 4 will be done to compare the measurement at week 12 with baseline, week 4 and week 8

Determination of Subjects for Analysis

All subjects that have follow-up visits after elevated night pacing was programmed OFF. This will include subjects completed 12 weeks of follow-up and subjects that had elevated night pacing programmed OFF at 4 weeks and completed 8 weeks of follow-up.

7.9.9. Additional Exploratory Analyses

As this is a feasibility study with a relatively small sample size and no correction for multiple comparison, the ancillary objectives stated above were limited to the most likely possible outcomes predicted by the high rate pacing under investigation. There are many other potential exploratory analyses that could be of interest and could be performed. Foremost, although not explicitly stated in the protocol, it is possible that there might be no effect of the therapy at the 4 week follow-up visit, but that there is an effect of the therapy at the 8 week visit – particularly for those subjects with high rate pacing kept programmed to ON at the 4 week follow-up visit. Particularly for, but not limited to, any measurement that was trending towards significance at week 4, it will be of interest to test the 8 week measurement against the baseline measurement for significance of the change from baseline. If done, these tests should be performed analogously to the 4 week tests described within this section.

7.10. Changes to Planned Analysis

There were a number of minor errors in the Statistical Design and Methods section of Version 3.0 of the REVAMP CIP. These errors include formatting issues, incomplete information and incorrect references. None of these issues require a change in the planned analysis specified in the CIP. These issues have been corrected in the SAP. The issues that have been identified include

- There is a reference to the MNLWHF score in the 8 week 6 Minute Walk Test Distance endpoint in the Analysis Methods section. The measured outcome should be distance rather than MNLWHF score.

In the event that the CIP is revised, the errors specified in this section should be updated in that revision.

8. Validation Requirements

All safety objectives will be validated at least at level II validation (peer review). Efficacy objectives will be validated at least at level III validation (self-validation). Any results used for abstracts or presentations may be validated at a more rigorous level.

9. References

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