Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	MARVEL 2 (Micra Atrial TRacking Using A Ventricular AccELerometer 2)
Clinical Investigation Plan Identifier	MARVEL 2 study (MDT18024)
Clinical Investigation Plan Version	MARVEL 2 CIP version 2
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Document Reference Number	Not applicable

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not applicable, new version	Vince Splett, Principal Scientist Francesca Lemme, Senior Statistician Kurt Stromberg, Senior Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
A3	Accelerometer signal associated with passive ventricular filling (associated with E-wave on echo)
A4	Accelerometer signal associated with active ventricular filling (associated with A-wave on echo)
ADC	Analog-to-digital converter
AE	Adverse event
ANOVA	Analysis of variance
AV	Atrioventricular
BPM	Beats per minute
CIP	Clinical investigation plan
csv	Comma-separated values
DDD pacing mode	Sensing and pacing occurs in both the atrium and in the ventricle
ECG	Electrocardiogram
e-CRF	Electronic case report form
EGM	Electrogram
LVOT	Left ventricular outflow tract
PR interval	Time between P-wave and R-wave
R	R programming language for statistical computing
SAS	SAS Institute (SAS software)
SD	Secure digital
TPS	Transcatheter pacing system
VDD pacing mode	Sensing occurs in the atrium and in the ventricle, while pacing is limited to the ventricle. In VDD, pacing is synchronized to atrial sensing. In the absence of atrial activity, VVI pacing behavior is seen. The ventricle is paced synchronously to the atrium up to the programmed maximum tracking rate. MARVEL 2 adaptive mode pacing implements VDD pacing based on mechanical sensing of the atrial contraction.
VDI pacing mode	Sensing occurs in the atrium and in the ventricle, while pacing is limited to the ventricle. In VDI, pacing is not synchronized to atrial sensing. The behavior is similar to VVI pacing. The ventricle is paced asynchronously to the atrium up to the programmed maximum tracking rate.
VP	Ventricular pace
VS	Ventricular sense
VTI	Velocity time integral
VVI pacing mode	Sensing and pacing occur only in the ventricle.
VVIR pacing mode	Rate adaptive VVI pacing

3. Introduction

The Micra™ TPS was developed to provide pacing entirely within the right ventricle to minimize or eliminate the acute and chronic complications related to the leads and pocket in traditional transvenous pacing systems.[1,2] In a cohort of 726 implants with a median follow-up of 16.9 months, Micra ™ TPS had a system or procedure major complication rate that was nearly half that observed in studies of traditional transvenous pacing systems. These results have been maintained in real-world settings.[3] Currently, Micra is approved for use in all geographies where the MARVEL 2 study will be conducted, specifically: US, Europe, and Asia. Micra also provides rate response via a 3-axis intracardiac accelerometer.[4] However, the majority of patients requiring pacing are not recommended for VVI pacing. Other pacing modalities including VDD or DDD are recommended for patients with atrioventricular (AV) block and normal sinus node function where there is a need to preserve atrioventricular synchrony.[5] Thus, the majority of patients with AV block cannot currently benefit from current intracardiac pacemakers.

The MASS/MASS2 studies collected the intracardiac accelerometer signal from 39 subjects with an implanted Micra device and intrinsic AV conduction during the study period. These studies showed that four distinct signals, including a signal for atrial contraction (designated A4) could be observed.[6] Accelerometer signals from these subjects were used to develop an algorithm to provide AV synchronous pacing. That algorithm was evaluated in the MARVEL study. The MARVEL study demonstrated improved atrioventricular synchronous pacing in humans using Micra's intracardiac accelerometer to mechanically detect atrial contraction. Specifically, a total of 64 subjects completed the MARVEL study procedure at 12 centers in 9 countries. The MARVEL study showed that the average AV synchronous pacing percentage was 87.0% (95% CI: 81.8% - 90.9%) across all subjects and 80.0% in subjects with high-grade (i.e. persistent) AV block. In subjects with high-grade AV block the AV synchrony during AV synchronous pacing was greater than the 37.5% observed during VVI pacing ($p<0.001$).[6] The MARVEL study also demonstrated that VDD pacing based on mechanical atrial sensing was safe. A small sub-study of the MARVEL study, MARVEL-Evolve, re-tested the MARVEL algorithm in 9 patients from one center to collect and compare the accelerometer signals and AV synchrony at two time-points. The mean time between visits was 7.1±0.6 months. MARVEL-Evolve showed no evidence of a difference in the percentage of AV synchrony during rest between study visits ($p=0.740$). There was no difference in the A4 amplitude during rest between visit 1 (205.7 mG, 95% CI: 97.9 – 313.6 mG) and visit 2 (207.1 mG, 95% CI: 91.9 – 322.4 mG, $p=0.933$).

The accelerometer signal is complex and currently is not well understood by clinicians. Therefore, it is desirable to reduce the clinical burden and expertise required to accurately set up the accelerometer detection algorithm. To accomplish this, Medtronic enhanced the MARVEL algorithm to automatically adjust the most often programmed detection parameters. In addition, two mode-switching algorithms were incorporated: (1) a mode-switch to VVI-40 for patients with paroxysmal AV block who often have intact AV conduction and (2) a mode-switch algorithm that switches to VVIR (rate adaptive pacing) if the sensor rate is significantly faster than the VDD rate. The performance of these algorithm enhancements and the overall AV synchrony achieved by the enhanced AV algorithm are the focus of the MARVEL 2 study.

4. Study Objectives

4.1 Primary Objective(s)

4.1.1 Primary Efficacy Objective

Demonstrate the superiority of the MARVEL 2 features to provide atrioventricular synchronous pacing relative to Micra VVI pacing in subjects with normal sinus node function and persistent 3rd degree AV block at rest.

4.1.2 Primary Safety Objective

Demonstrate that the MARVEL 2 features provide pacing as intended.

4.2 Secondary Objective

Demonstrate an increase in stroke volume, as measured by left ventricular outflow tract velocity time integral, with the MARVEL 2 features compared to VVI pacing in subjects with normal sinus node function and persistent 3rd degree AV block.

5. Investigation Plan

5.1 Study Design

The MARVEL 2 study is an acute, prospective, global, multi-center, software-download clinical study to evaluate the performance of the MARVEL 2 software, which includes a comprehensive set of the anticipated Micra AV features. The study is planned to be conducted in the US, Europe and Asia. In the United States, the study is being conducted under an Investigational Device Exemption (IDE). Overall, the study is expected to be conducted at approximately 15-20 centers and will enroll up to 100 subjects to obtain at least 70 usable Holter datasets to meet the sample size required to test the primary objectives of the study. Holter datasets will be considered usable if there is readable telemetry signal as determined by Medtronic personnel experienced in the review of Holter recordings.

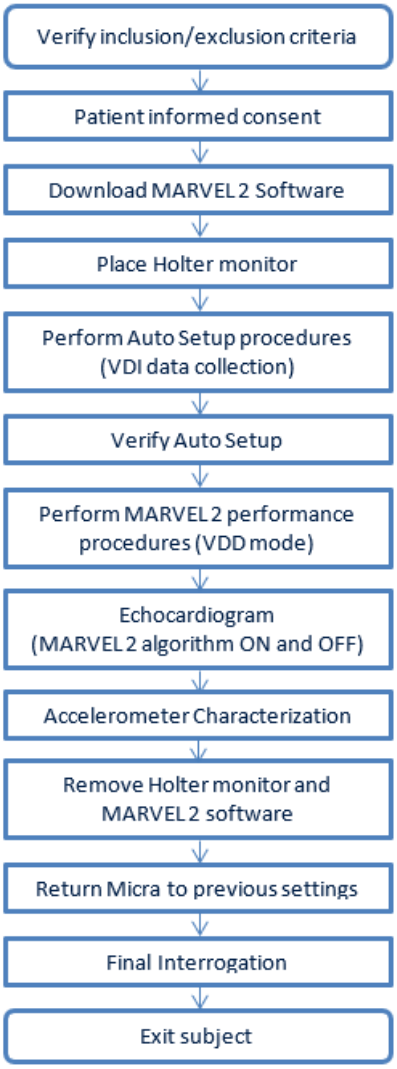
The expected total study duration (from first subject enrollment to the exit of the last subject) is approximately 6-months. This represents the time necessary to enroll the target sample size of at least 70 subjects. A download study into patients with an existing Micra device allows the new algorithm performance to be measured in patients where a Micra device has already been chosen as most appropriate for the patient. Most enrolled subjects will complete the study procedures at a single 2 to 4-hour study visit. However, a subset of subjects who enroll in the study at the time of their Micra implant (anticipated to be approximately 10 subjects) will have the investigational algorithm downloaded following Micra implant, one day post-implant, and at approximately 1-month post-implant. Studying these subjects with *de novo* Micra implants will allow the MARVEL 2 software features to be tested at multiple points in the device life cycle.

Additionally, study centers that participated in the MARVEL study may enroll up to three randomly selected subjects with normal sinus node function and persistent 3rd degree AV node block that participated in the MARVEL study. Allowing subjects enrolled in the MARVEL study to participate in the MARVEL 2 study will enable an assessment of AV synchrony at multiple points in time.

Because the download algorithm running in Micra device significantly increases current drain, a 2 to 4-hour acute study is used to limit the reduction in device longevity.

Figure 1 displays the MARVEL 2 study flow for all study subjects.

Figure 1: MARVEL 2 Study Flow



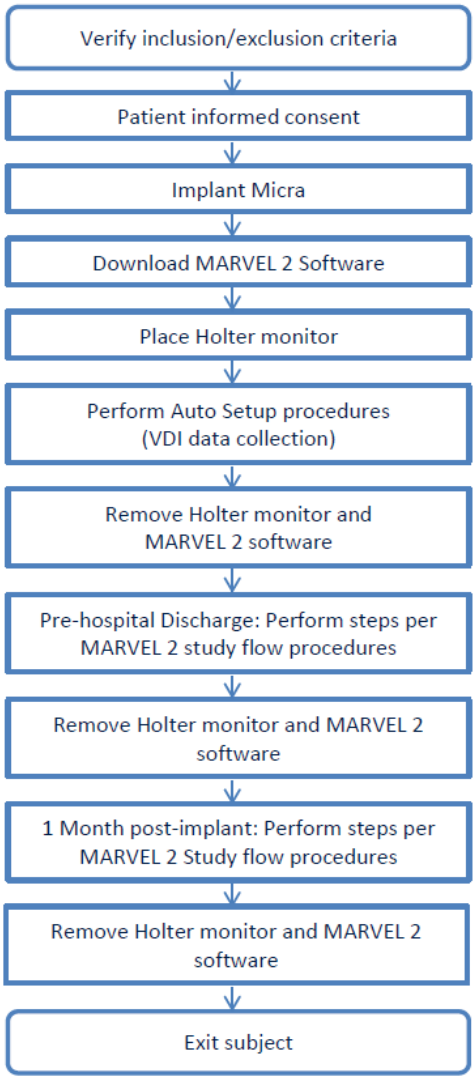
5.1.1 De novo subjects

De Novo subjects are those subjects that enroll in the MARVEL 2 study at the time of their Micra implant. Note that these will be subjects where the clinician and patient have determined that a Micra device is the most appropriate therapy for the patient's condition. It is expected that approximately 10 *de novo* subjects will enroll in the MARVEL 2 study. Studying these subjects with *de novo* Micra implants ensures some accelerometer signals are collected during or immediately after the implant procedure. In addition, studying these subjects prior to hospital discharge and at 1-month provides information on the evolution of the accelerometer signal and AV synchrony.

Specifically, following Micra implant and initial device interrogation, the investigational MARVEL 2 software will be downloaded into the Micra and a custom Holter monitor will be placed on the subject. The Holter monitor will record surface ECG, EGM, accelerometer signals, and device and MARVEL 2

algorithm markers. The subject should be in a sitting or supine position while the automatic setup runs for approximately 20 minutes. Once completed, the MARVEL 2 software will be removed from the Micra and Holter monitor removed from the subjects. Note that the MARVEL 2 software will be in monitor mode (VDI mode with no atrial tracking) on the day of the Micra implant. Prior to hospital discharge and at approximately 1-month post-implant *de novo* subjects will perform the MARVEL 2 study procedures as described in Figure 2.

Figure 2: Additional Study Procedures for De Novo Subjects



5.1.2 Reenrollment of MARVEL study subjects

Study centers that participated in the MARVEL study can reenroll up to 3 subjects in the MARVEL 2 study from their subjects who had normal sinus node function and persistent 3rd degree AV block during Holter monitoring in the MARVEL study. To avoid selection bias when considering reenrollment, centers

that had 3 or fewer eligible subjects are required to approach all their eligible subjects for reenrollment while centers with more than 3 eligible subjects will be given a randomly permuted list of subjects to approach for reenrollment in MARVEL 2 (note that these centers are required to approach the subjects in order of their permuted list until up to 3 subjects are reenrolled). Based on this strategy, a maximum of 24 reenrollments may occur if all MARVEL centers participate in MARVEL 2 and all eligible MARVEL subjects enroll in the MARVEL 2 study (note, not all centers had 3 eligible subjects).

5.2 Study Population

The target population will consist of patients ≥18 years in age, with documented history of AV block, and implanted with a Micra with remaining device longevity of 6 years or more or expected to be implanted with a Micra.

5.3 Study Procedures

Study procedures for subjects with existing Micra devices will be conducted in a one day in-office visit. Study procedures for *de novo* subjects with a new Micra implant will be conducted over a 1-month period to collect the study procedures at up to 3 points in time. Data collection specific for the MARVEL 2 study are summarized in Table 1.

Table 1: Summary of Study Procedures

MARVEL 2 Study Data Collection	Micra In-clinic Subject		Micra De Novo Subject			
	Baseline	MARVEL 2 Procedure	Baseline	Implant	Pre-Hospital Discharge MARVEL 2 Procedure	1 month-MARVEL 2 Procedure
Inclusion/exclusion assessment	X		X			
Patient informed consent	X		X			
Demographics and pacing indication	X		X			
Medical history	X		X		X	X
Micra Implant				X		
Cardiovascular medications	X		X		X	X
Physical Examination	X		X		X	X
12 Lead ECG	X		X		X	X
X-Ray image(s) of Micra implant location	X[1]		X[1]			
Initial device interrogation Save to media		X		X	X	X
Download MARVEL 2 software		X		X	X	X
Holter monitoring (Auto Set-up phase) VDI data collection Selects best vector combination Selects sensing parameters		X		X	X	X
Holter monitoring (In-clinic Evaluation phase) Perform quiet resting period Perform posture testing and hall walks Accelerometer Characterization		X			X	X
Echocardiogram		X			X	X
Remove MARVEL 2 software		X		X	X	X
Final device interrogation Save to media		X		X	X	X
Study exit		X				X
Adverse Events	If Occur					
Study Deviations						
Device Deficiencies						
System Modification						

[1]If available. If not available, no additional x-ray images will be collected.

6. Determination of Sample Size

A sample size of at least 70 subjects with usable Holter datasets, of which at least 35 have a predominant rhythm of persistent 3rd degree AV block with normal sinus function, is required to test the study's primary objectives. For details of the sample size calculation see Sections 7.5.3.5, 7.5.4.5, and 7.5.5.5.

7. Statistical Methods

7.1 General Considerations

7.1.1 Report for which this Statistical Analysis Plan Applies

[redacted] This SAP applies to the final study report and to any publication(s) reporting the results of the MARVEL 2 primary and secondary objectives.

7.1.2 Analysis Timing

There will be one formal analysis of the study's primary, secondary, [redacted] objectives, which will occur once all enrolled subjects have had the opportunity to complete the study and the study databases have been locked.

7.1.3 Type I Error Control

For the study to be considered a success, the null hypothesis for both the primary efficacy and safety objectives must be rejected. Additionally, to make a statistically valid claim of significance for the secondary objective, the null hypothesis for both primary objectives must be rejected and the null hypothesis for the secondary objective must be rejected. This testing strategy guarantees a study wide type I error rate of 0.05.

7.1.4 Usable Holter Datasets

A Holter dataset (i.e. device data telemetered to the Holter flash memory and surface ECG recordings) will be considered usable if there is readable telemetry signal as determined by the presence of visible device and algorithm marker channel. Additionally, to be included in the analysis of study objectives that require assessment of AV synchrony (i.e. primary efficacy objective, [redacted] visible P-waves must be present on the ECG recordings.

7.1.5 Determination of Predominant Heart Rhythm

Holter data from the approximately 20-minute auto-setup phase will be used to determine each subject's predominant heart rhythm during the Holter monitoring session. The sinus node function will be categorized as normal sinus, sinus node dysfunction (sinus bradycardia, sinus tachycardia, other) or atrial arrhythmia. The AV conduction status will be categorized as persistent 3rd degree AV block or

intact AV conduction. Note that subjects with a predominant rhythm of persistent 3rd degree AV block with normal sinus function will be included in the analysis of the primary efficacy objective.

[redacted]

[redacted]

7.2 General Summaries

7.2.1 Baseline and Medical History

Standard baseline and relevant medical history will be collected on the e-CRFs for all enrolled subjects. Baseline and medical history variables to be summarized include, but are not limited to: age, sex, cardiovascular history, arrhythmia history, and cardiovascular medications.

For continuous variables, mean, standard deviation, median, and range will be reported. For categorical variables, frequency and percentage will be reported. Baseline information will be summarized for all enrolled subjects and for subjects with usable Holter data. Additionally, baseline and medical history will be summarized for the following subsets of subjects:

1. Subjects included in the analysis of the primary efficacy objective (i.e. those with a predominant rhythm during Holter monitoring of persistent 3rd degree AV block)

[redacted]

7.2.2 Clinical Investigation Plan (CIP) Deviations

Deviations from the clinical investigation plan will be collected as deviations on the Study Deviation e-CRF as they occur. Deviations will be summarized in a table by category. The number of deviations per category, and the number and percentage of subjects with a deviation in each category will be reported.

7.2.3 Adverse Events

All adverse events regardless of severity or relationship to the MARVEL 2 algorithm will be collected during the study on the Adverse Event e-CRF as they occur. Section 7.5.6.7 describes the methods that will be used to summarize adverse events.

7.2.4 Subject Disposition

The number of enrolled subjects and number of subjects with usable Holter data will be reported by study center and country.

The number and percentage of enrolled subjects exiting the study will be summarized by subject status term on the Study Exit e-CRF. As the majority of subjects will complete the study procedures during a single study visit, premature study exit is not expected.

A narrative of any subject deaths occurring during the study period will be provided in the final study report.

7.3 Center Pooling

The study is expected to be conducted in approximately 15-20 centers in Europe, USA and Asia. Study results are not expected to differ by study center, therefore data from all centers will be pooled. There will be no minimum limit that each investigator must enroll. The maximum number of enrolled subjects per center is 20 subjects.

7.4 Interim Analyses

No interim analysis of the study objectives is planned for this study.

7.5 Evaluation of Objectives

7.5.1 Holter Data Preprocessing

Following download of the investigational MARVEL 2 software, a Holter monitor will be placed on the subjects for the duration of study procedures. The Holter monitor continuously records surface ECG, EGM, accelerometer signals, and device and MARVEL 2 algorithm markers are telemetered from the implanted Micra device. The marker channel includes the ventricular sensed and paced event markers as well as markers unique to the MARVEL 2 features including whether the MARVEL 2 features sense an atrial beat (A4 signal). In addition, the Holter records supplemental marker data from the Micra including V-V interval, pacing mode, pacing amplitude, and MARVEL 2 specific settings and measurements, including A4 amplitude and mode switch status.

[redacted]

[redacted]

[redacted]

Each Holter dataset will be reviewed by Medtronic personnel experienced in the review of Holter recordings to determine the recording time, quality of the recording, and confirm correct MARVEL 2 feature operation.

[redacted]

[redacted]

7.5.2 Initial Processing

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.5.3 Primary Efficacy Objective

Demonstrate the superiority of the MARVEL 2 features to provide atrioventricular synchronous pacing relative to Micra VVI pacing in subjects with normal sinus node function and persistent 3rd degree AV block.

7.5.3.1 Endpoint Definition

A subject will meet the primary efficacy endpoint if a paced or sensed ventricular beat is within 300 ms following an ECG confirmed P-wave for at least 70% of the ECG confirmed P-waves. The primary endpoint will be evaluated during the MARVEL 2 setup phase (VDI pacing which is effectively VVI pacing) and during the resting period in which the MARVEL 2 features are enabled.

Rationale for the endpoint is provided in section 8.2.1.1 of version 2 of the MARVEL CIP.

7.5.3.2 Hypothesis

H_o: $\pi_{AV} = \pi_{VVI}$, versus

H_a: $\pi_{AV} \neq \pi_{VVI}$

where π_{AV} is the is the proportion of subjects meeting the primary efficacy endpoint during MARVEL 2 adaptive mode (VDD) pacing, and π_{VVI} is the proportion of subjects meeting the primary efficacy endpoint in VVI mode.

7.5.3.3 Performance Requirements

The percentage of subjects meeting the primary endpoint in the MARVEL 2 adaptive pacing mode is significantly greater (at the 0.05 level) than the percentage of subjects meeting the endpoint in VVI pacing mode.

Meeting the performance requirement for the primary efficacy objective will demonstrate that the MARVEL 2 features provide high rates of atrioventricular synchronous pacing and greatly exceed rates

observed with VVI pacing in the patient population expected to benefit the most from atrioventricular synchronous pacing.

7.5.3.4 Analysis Methods

For each subject, the VVI pacing control period will occur shortly following investigational software download during the approximately 20-minute algorithm auto-setup phase where the MARVEL 2 programmable parameters are setup to enable optimal tracking of the A4 signal. The auto-setup phase will occur while the MARVEL 2 features are in monitor mode (i.e. VDI pacing which is effectively VVI pacing). For purposes of evaluating the primary efficacy objective, the 20-minute resting period while the MARVEL 2 features are programmed to adaptive mode and providing VDD pacing will serve as each subject's treatment period.

Note that a randomized crossover design will *not* be used to compare AV synchronous pacing percentage between the MARVEL 2 pacing mode and VVI pacing for the following reasons: 1) knowledge of pacing mode is unlikely to influence AV synchronous pacing rate as such knowledge is unlikely to influence right atrial contractility, 2) the auto-setup phase will provide an opportunity to assess the AV synchronous pacing percentage during VVI pacing, 3) carryover effects are not possible since as soon as the MARVEL 2 features are programmed to adaptive mode atrial tracking will commence, [redacted]

The accuracy spreadsheet derived from each Holter file (see section 7.5.2.3) will be used to determine the synchrony status (yes or no) for each P-wave. Each accuracy spreadsheet will be imported into SAS and/or R and the P-P interval computed for each P wave *i* (where *i*>1) as the time in seconds in Column 1 (A) for the i^{th} P-wave minus the time in seconds in Column 1 (A) for the i^{th}-1 P-wave. Each P-wave in the accuracy spreadsheet file will be classified as being evaluable or not evaluable. P-waves that are not evaluable include:

1. P-waves with no ventricular sense or pace markers and indication of telemetry dropout in the first 300 ms after the P-wave. These are identified from the accuracy spreadsheet where column 13 (M) = 0 and column 14 (N) = 1.
2. P-waves that occur during an AV conduction mode switch as these P-waves occur when the pacing mode is set temporarily to VDI40 while the device checks for intrinsic AV conduction. These are identified from the accuracy spreadsheet where a supplemental marker in the preceding P-P interval (column 15 (O) < P-P interval), and the pacing mode in the supplemental marker is VDI40, indicating a mode switch (column 17 (Q) = 7). Note that for the pacing mode, the supplemental marker indicates the pacing mode on the next ventricular event, which is why a look-back to the preceding supplemental marker is necessary to determine if the current ventricular event is in a mode-switched state.

All other P-waves in the accuracy spreadsheet will be considered evaluable. Evaluable P-waves will be considered synchronous if they occur within 300 ms of the following ventricular event. Thus, evaluable P-waves will be considered synchronous if column 2 (B) < 0.3 and asynchronous if column 2 (B) ≥ 0.3.

For the analysis of the primary efficacy objective, P-waves with records in the accuracy spreadsheet corresponding to the auto setup phase (i.e. columns 11 (K) and 12 (L) indicate auto setup phase) or

resting phase (i.e. columns 11 (K) and 12 (L) indicate auto setup phase) will be selected. The auto setup phase will occur during MARVEL 2 monitor mode pacing (i.e. VVI pacing) and the resting phase will occur during MARVEL 2 adaptive mode pacing (i.e. VDD pacing). If at least 70% of evaluable beats are considered synchronous during the VVI or MARVEL 2 adaptive pacing mode during resting, then the subject will be considered to have met the primary efficacy endpoint during the VVI or MARVEL 2 adaptive pacing mode during rest respectively. McNemar's test for paired proportions will be used to test the primary efficacy objective hypothesis. Note that subjects with fewer than 500 evaluable beats during each period will be excluded from the primary efficacy analysis.

[redacted]

The following pre-specified subgroups will be evaluated: sex, geography (US versus outside of US), and participation in the MARVEL study (yes versus no). A repeated measures logistic regression model using generalized estimating equations will be used to evaluate the homogeneity of the MARVEL 2 adaptive pacing mode effect on the primary efficacy endpoint by subgroup. For this model, the response will be the primary endpoint status (1=met primary endpoint, 0=did not meet) and the independent variables will be the pacing mode (VVI pacing or MARVEL 2 adaptive mode), subgroup status, and a subgroup status by pacing mode interaction.

[redacted]

[redacted]

Additionally, the proportion of subjects meeting the primary efficacy endpoint will be summarized and compared between VVI pacing and MARVEL 2 adaptive pacing using the methods described above in the following subsets of subjects with normal sinus node function and persistent 3rd degree AV block:

1. Those subjects exhibiting low PVC burden (<5% of cardiac cycles demonstrating evidence of PVC)
2. Those subjects exhibiting low PVC burden with a mitral valve doppler echo E/A ratio of 1.5 or less

7.5.3.5 Sample Size Calculation

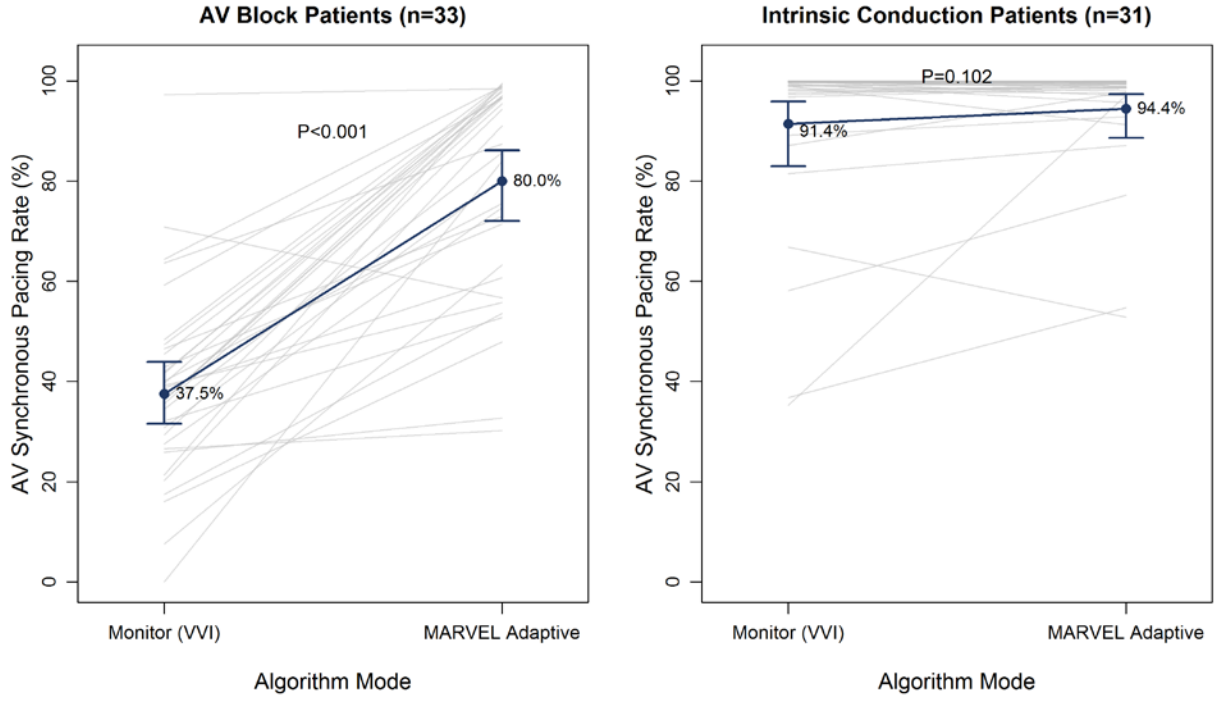
A sample size of at least 35 subjects with normal sinus node function and persistent 3rd degree AV block and at least 500 evaluable cardiac cycles during the auto setup and 20-minute resting period will provide greater than 90% power to reject the null hypothesis based on the following assumptions:

1. Two-sided type I error rate = 0.05
2. Single analysis after all enrolled subjects have had an opportunity to complete the MARVEL 2 study procedures and have had their Holter data evaluated
3. Each subject will have at least 500 evaluable beats during the auto-setup phase (VVI pacing) period and during VDD pacing during the 20-minute resting period
4. The proportion of subjects meeting the primary efficacy endpoint in one pacing mode, but not the other (i.e. proportion of discordant pairs) will exceed 50%
5. At least 90% of discordant subjects will favor the MARVEL 2 features

Justification of Sample Size Assumptions

Figure 9 displays the AV synchronous pacing percentage observed in the MARVEL study by predominant rhythm. The average AV synchronous pacing percentage among the 33 subjects with a predominant rhythm of high-grade AV block was 80.0% during MARVEL adaptive mode (VDD pacing) compared to 37.5% during VVI pacing (P<0.001). Among the 33 subjects with a predominant rhythm of high-grade AV block, 72.7% of subjects (24 of 33) had an AV synchronous pacing rate exceeding 70% while in MARVEL adaptive mode compared to 6.1% (2 of 33) during MARVEL monitor mode (VVI pacing).

Figure 9: AV Synchronous Pacing Percentage Observed in the MARVEL Study by Predominant Rhythm



7.5.3.6 Determination of Subjects/Data for Analysis

All subjects with normal sinus node function and persistent 3rd degree AV block during Holter monitoring with at least 500 evaluable beats during VVI pacing and at least 500 evaluable beats during MARVEL 2 adaptive pacing in which the device is providing VDD pacing will be included in the primary analysis for this objective. For *de novo* subjects, only data collected during the 20-minute resting period at the pre-hospital discharge procedure will contribute to the analysis of the primary objective. [redacted] However, if a *de novo* subject does not have usable Holter data from the pre-hospital discharge procedure, their Holter data at the 1-month post-implant procedure will be used in the analysis, if available.

As described in section 7.5.3.4 cardiac cycles with no ventricular sense or pace markers and indication of telemetry dropout in the first 300 ms following a P-wave as well as P-waves that occur during an AV conduction check will be excluded from the primary analysis (i.e. they are not evaluable beats).

7.5.3.7 Missing Data and Sensitivity Analyses

Missing Data

Given the relatively short duration of the study, missing data is not expected to be a serious issue. Since telemetry dropout may influence the number of evaluable beats for a subject during both VVI pacing

and MARVEL 2 adaptive pacing, the total number of heart beats and total number of evaluable beats will be summarized.

Missing Data Sensitivity Analyses

If any subjects with normal sinus node function and persistent 3rd degree AV block do not have usable Holter data during the study, the reason the Holter data was not usable will be discussed. Additionally, to address concerns with missing data that may arise, sensitivity analyses will be performed to assess the robustness of the observed statistical inference with respect to the missing data.

The first sensitivity analysis will be to include all subjects with normal sinus node function and persistent 3rd degree AV block that had some usable Holter data during both 20-minute resting period (MARVEL 2 adaptive pacing) and VVI pacing control period (i.e. auto-setup phase) regardless of the number of evaluable beats in each phase.

The second sensitivity analysis will include all subjects who had the MARVEL 2 software downloaded and had a Holter monitor placed on them that were classified as having a predominant rhythm of persistent 3rd degree AV block with normal sinus function or who did not have their rhythm classified. This sensitivity analysis will incorporate a tipping point methodology. Specifically, all subjects with missing data will be included as meeting the primary efficacy endpoint during MARVEL 2 adaptive pacing and not meeting it during VVI pacing (i.e. discordant in favor of MARVEL 2 adaptive pacing) and then iteratively changed to not meeting the endpoint during MARVEL 2 adaptive pacing and meeting it during VVI pacing (i.e. discordant in favor of VVI pacing pacing). The tipping point will be defined as the number of subjects of the total with missing data that would have to shift from being discordant in favor of MARVEL 2 pacing to discordant in favor of VVI pacing to change the statistical inference. If the tipping point is less than the number of subjects with missing data stochastic methods may be used to aid in interpreting the likelihood of meeting or exceeding the tipping point as follows. Using the observed data, the beta distribution will be used to draw the probability a subject with missing data has normal sinus node function and persistent 3rd degree AV block. Next, the Dirichlet distribution with shape parameters corresponding to the observed 2×2 table will be used to draw the probability that the subject with missing data would be in the table cell that is discordant and in favor of VVI pacing. The product of these two probabilities will be used to determine the number of subjects with missing data that would end up in the discordant cell in favor of VVI pacing. Monte-Carlo sampling will be used to determine the probability that the tipping point is met or exceeded.

Other Sensitivity Analyses

Since *de novo* subjects may have more than one visit in which both the AV synchronous pacing percentage is evaluated in both VVI and MARVEL 2 adaptive mode, the primary efficacy endpoint will also be compared utilizing usable Holter data from all study visits for subjects with normal sinus node function and persistent 3rd degree AV block. Specifically, a logistic regression model utilizing GEE to account for correlation in outcomes within subject will be used to estimate the effect of MARVEL 2 adaptive pacing on the primary efficacy endpoint. Specifically, the response for this model will be the primary efficacy endpoint status (1=met primary efficacy endpoint, 0=did not meet primary efficacy endpoint) and the independent variable will be pacing mode (VVI or MARVEL 2 adaptive mode). An exchangeable working correlation matrix will be employed with subjects considered repeated across

pacing mode and study visit. The SAS code for implementing the model is similar to that shown above for the subgroup analyses with the exception that the indicator for adaptive mode pacing would be the only covariate.

[redacted]

7.5.4 Primary Safety Objective

Demonstrate that the MARVEL 2 features provide pacing as intended.

7.5.4.1 Endpoint Definition

A subject will meet the primary safety endpoint if they are free from the following MARVEL 2 software related events during the entire Holter monitoring period where the MARVEL 2 features are enabled:

1. Pauses lasting longer than two cardiac cycles (where cardiac cycle length is defined by the programmed lower rate interval), AND
2. Episodes of oversensing induced tachycardia exceeding 3-minutes, defined as oversensing accelerometer signal leading to a heart rate exceeding 100 BPM

7.5.4.2 Hypothesis

H_o: $\pi_{AV} \leq 87\%$, versus

H_a: $\pi_{AV} > 87\%$

where π_{AV} is the percentage of subjects meeting the primary safety endpoint during the MARVEL 2 pacing mode.

7.5.4.3 Performance Requirements

The percentage of subjects meeting the primary safety endpoint is significantly greater than 87% (i.e. the lower two-sided 95% confidence interval for the estimate exceeds 87%). For example, in a sample size of 70 subjects with usable Holter datasets, this objective would be met if at least 67 of the 70 subjects (96%) meet the primary safety endpoint. Further, with a sample size of 70 subjects with usable Holter datasets the lower two-sided 95% confidence interval will be 94.9% if all 70 subjects meet the primary safety objective.

7.5.4.4 Analysis Methods

All available Holter recordings (including multiple recordings for subjects evaluated at multiple visits following initial Micra implant) will be used to determine if a subject meets the primary safety endpoint. The ventricular event spreadsheet derived from each Holter file (see section 7.5.2.4) will be used to determine the primary event status associated with each Holter recording. Each ventricular event spreadsheet will be imported into SAS and/or R.

The MARVEL 2 features will be considered enabled when column 6 (F) in the ventricular event spreadsheet has the values 5, 6, 7, or 14.

Next, the ventricular markers from the Micra device will be searched for long intervals. To accomplish this, the programmed lower rate interval will be computed by converting column 3 (C) to seconds by dividing 60 by the value in column 3 (C). Next, the difference in seconds between the current ventricular event and the next ventricular event will be calculated (i.e. the V-V interval). If this value exceeds twice the programmed lower rate interval and there is no telemetry dropout (i.e. column 4 (K) = 0) the event will be flagged for further investigation.

Similarly, the ventricular rate in seconds from one ventricular event to the next will be calculated and used to determine if the rate exceeds 100 bpm (0.6 seconds). If the time from the first ventricular event with a rate exceeding 100 bpm to the last ventricular event with a rate exceeding 100 bpm is greater than 3 minutes, the sequence of events will be marked for further investigation. Note that the ventricular rate associated with ventricular events where there is evidence of telemetry dropout (i.e. column 4 (K) = 1) will not be computed and the ventricular event will be ignored when computing the duration of rates exceeding 100 bpm. This strategy makes the implicit assumption that the higher rate continues through the telemetry dropout period unless the next pair of ventricular events has a rate

below 100 bpm. The telemetry protocol between the implanted Micra and the Holter monitor may result in duplicate ventricular event markers to be transmitted. This would result in multiple entries in the ventricular event spreadsheet with a non-physiological time between the ventricular events. Therefore, ventricular events occurring within 100 ms of a previous ventricular event will be discarded as they are non-physiological (e.g. correspond to a rate exceeding 600 bpm).

For each long interval event identified above, the surface ECG signals and EGM will be manually reviewed to determine if they are true pauses or due to telemetry dropout. For any true pauses, the surface ECG signal, accelerometer signal, and device markers will be examined to determine if the pause was related to the MARVEL 2 algorithm or for another reason (e.g. R-wave undersensing).

Similarly, for each high heart rate event, the surface ECG, the accelerometer signal, and MARVEL 2 markers will be examined to determine if the high heart rates were induced by MARVEL 2 algorithm oversensing or for some other reason (e.g. appropriate rate response, T-wave oversensing). Subjects free from pauses and oversensing induced tachycardia exceeding 3 minutes related to the MARVEL 2 algorithm will be considered to have met the primary safety endpoint.

An exact binomial test will be used to test the primary safety hypothesis. Specifically, the numerator will be the number of subjects meeting the primary safety endpoint. The denominator will be the number of subjects with Holter recordings with usable telemetry while the MARVEL 2 algorithm is downloaded.

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The following pre-specified subgroups will be evaluated if there are two or more subjects who do not meet the primary safety objective: sex, geography (US versus outside of US), and predominant heart rhythm during Holter recording (normal sinus node function and persistent 3rd degree AV block, intact

AV conduction, or other predominant rhythm). Fisher's exact test will be used to identify differences between subgroups.

7.5.4.5 Sample Size Calculation

A sample size of 70 subjects with usable Holter telemetry data during the MARVEL 2 study procedures provides at least 90% power to test the primary safety hypothesis given the following assumptions:

1. One-sided type I error rate = 0.025
2. Single test of a proportion after all enrolled subjects have had an opportunity to complete the MARVEL 2 study procedures and have had their Holter data evaluated.
3. The proportion of subjects meeting the primary endpoint in the MARVEL 2 pacing mode will exceed 98%.

Justification of Sample Size Assumptions

It is expected that all (100%) subjects will meet the primary safety endpoint. Specifically, in the MARVEL study, no pauses exceeding two cardiac cycles (as defined by the lower pacing rate interval) and no oversensing induced tachycardia exceeding three minutes were observed.

7.5.4.6 Determination of Subjects/Data for Analysis

All available Holter recordings (including multiple recordings for subjects evaluated at multiple visits following initial Micra implant) with usable telemetry during MARVEL 2 adaptive mode will be included in the analysis.

7.5.4.7 Missing Data and Sensitivity Analyses

The primary source of missing data for this objective is anticipated to be Holter usability status and telemetry dropout during MARVEL adaptive mode pacing. Note that both sources of missing data can plausibly be assumed independent of primary safety endpoint status as Holter usability status is primarily related to electrode contact. However, to quantify the amount of missing data, the number of unusable Holter files and the proportion of beats during MARVEL 2 operation with telemetry dropout will be computed.

If Holter data from subjects who had the MARVEL 2 software downloaded is missing (e.g. deemed entirely unusable, Holter never placed on subject), it will be included in a tipping point analysis to determine the sensitivity of the statistical inference to the missing data. If the tipping point is less than the number of subjects with missing data, stochastic methods may be employed to aid in interpreting the likelihood the tipping would be achieved. Specifically, simulations from a Beta distribution with shape parameters based on the observed data will be used to compute the predictive probability of observing or exceeding the tipping point.

7.5.5 Secondary Objective

Demonstrate an increase in stroke volume, as measured by left ventricular outflow tract velocity time integral, with the MARVEL 2 software relative to VVI pacing in subjects with normal sinus node function and persistent 3rd degree AV block.

7.5.5.1 Endpoint Definition

The secondary endpoint is left ventricular outflow tract velocity time integral (LVOT VTI) as obtained from echocardiogram while the MARVEL 2 features are in adaptive mode (VDD pacing) and while the MARVEL 2 features are in monitor mode (VDI pacing which is effectively VVI pacing). This will be measured by the echo core laboratory.

7.5.5.2 Hypothesis

H_o: $\mu_{AV} = \mu_{VVI}$, versus

H_a: $\mu_{AV} \neq \mu_{VVI}$

where μ_{AV} is the population mean LVOT VTI in the MARVEL 2 adaptive pacing mode and μ_{VVI} is the population mean LVOT VTI in MARVEL monitor mode (VVI pacing).

7.5.5.3 Performance Requirements

The sample mean LVOT VTI during MARVEL 2 adaptive pacing (VDD pacing) is significantly different and greater at the 0.05 level than the sample mean LVOT VTI during VVI pacing.

Meeting the performance requirement for the secondary objective will demonstrate that the MARVEL 2 features can increase cardiac stroke volume compared to VVI pacing in the population with normal sinus node function and persistent 3rd degree AV block.

7.5.5.4 Analysis Methods

Echocardiograms will be collected for each subject during MARVEL 2 adaptive pacing and during VVI pacing. To ensure that the echo core lab is blinded to subject and programmed pacing mode, randomly generated numbers will be used to label the echo recording medium. Specifically, a random 5-digit number ("echo id") will be assigned to label the echo recording medium and link the echo core lab results to an individual study subject. Additionally, to address any possible order effects, study sites will be randomized to perform the echo while the MARVEL 2 algorithm is programmed to Adaptive mode first followed by Monitor Mode second or while the MARVEL 2 algorithm is programmed to Monitor mode first followed by Adaptive mode. This strategy will blind the echo core lab personnel to study site, subject, and pacing mode and allow the "echo id" to link to the appropriate center, subject, and pacing mode.

The echo core lab will determine LVOT VTI for up to 6 cardiac cycles per programmed mode and record their measurements on the echo corelab e-CRF. For each subject, the mean LVOT VTI will be computed within each MARVEL 2 programmed mode. Since subject is the experimental unit, a paired t-test will be used to test the null hypothesis. [redacted]

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The following pre-specified subgroups will be evaluated using an analysis of variance (ANOVA) model: sex, geography (US versus outside of US), and participation in the original MARVEL study (yes versus no). For each ANOVA model the response will be the change in LVOT VTI between MARVEL 2 adaptive pacing and VVI pacing. The independent variable will be an identifier for subgroup.

If graphical assessments (e.g. Q-Q plots) of the distribution of change in LVOT VTI strongly suggest a deviation from normality, the Wilcoxon Signed-Rank test may be used as a sensitivity analysis.

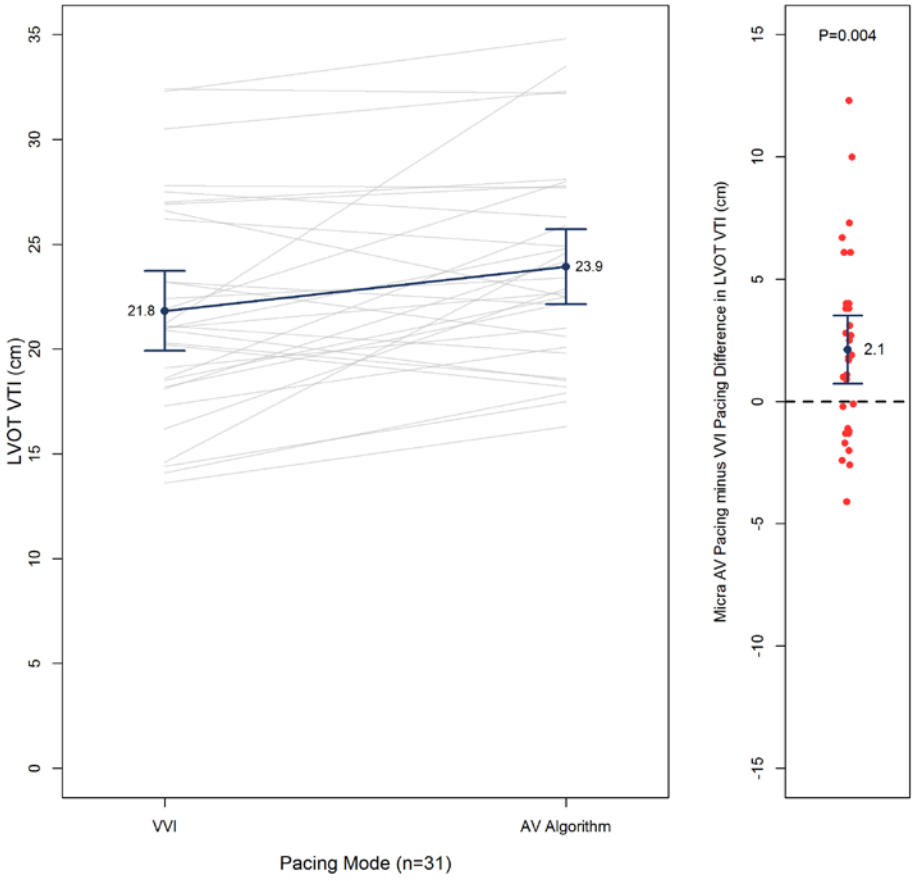
7.5.5.5 Power Calculation

Background

The MARVEL study demonstrated a mean increase in LVOT VTI of 2.1 (cm) [95% CI: 0.7 – 3.5 cm] with associated standard deviation of 3.8 cm in MARVEL 2 adaptive pacing relative to VVI pacing in 31 subjects with high-grade AV block and with paired echocardiogram data. Specifically, as displayed in Figure 10, mean LVOT VTI increased from an average of 21.8 cm to 23.9 cm. The left panel of Figure 10 displays the LVOT VTI values for individual subjects (gray lines) and on average (dark blue lines) for the 31 subjects with high-grade AV block subjects in MARVEL with paired echo assessments in both pacing modes. The right-hand plot in Figure 10 displays the absolute change in LVOT VTI for MARVEL 2 adaptive pacing relative to the VVI pacing mode for individual subjects (red circles) and on average (blue circle). The right-hand plot also indicates that the lower 95% confidence interval for the mean change in LVOT VTI exceeded zero.

The increase of 2.1 cm in LVOT VTI observed in the MARVEL study with MARVEL adaptive mode relative to VVI pacing is consistent with historical studies during the 1980s evaluating cardiac output between DDD and VVI pacing modes. See for example, Labovitz, et al[8], who observed a mean increase in LVOT VTI of approximately 2 cm with DDD pacing relative to VVI pacing in 26 patients with paired echocardiogram data in both DDD and VVI pacing modes.

Figure 10: LVOT VTI (cm) During VVI Mode and MARVEL Adaptive Mode (MARVEL Study)



Note: Error bars represent 95% confidence intervals for mean LVOT VTI by pacing mode (right panel) or in mean paired LVOT VTI value differences during MARVEL adaptive pacing relative to VVI pacing.

Power Calculation

As the sample size for the primary efficacy objective determines the number of subjects with normal sinus node function and persistent 3rd degree AV block with usable Holter data that are required for the study (at least 35 subjects), the power to reject the null hypothesis for the secondary objective was determined for a number of sample sizes as the protocol does not preclude study investigators from enrolling a higher number of subjects with normal sinus node function and persistent 3rd degree AV block nor account for the potential of missing echocardiogram data due to reasons such as improper

echocardiogram image acquisition, equipment malfunction, or subject refusal. The following assumptions were made for all power calculations:

1. Two-sided type I error rate = 0.05
2. Single analysis after all enrolled subjects have had an opportunity to complete the MARVEL 2 study procedures and have had their Holter data evaluated
3. Each subject will have paired echocardiogram available for analysis in both the MARVEL 2 adaptive mode and in VVI mode
4. The paired difference in LVOT VTI is normally distributed with a mean of 2.1 cm and a standard deviation of 3.8 cm in the population of potential patients with normal sinus node function and persistent 3rd degree AV block
5. A paired t-test will be the primary test statistic

Table 2 displays the study power for both the paired t-test and for the Wilcoxon Signed-Rank test when there are 30, 35, and 40 subjects with normal sinus node function and persistent 3rd degree AV block observed during Holter monitoring. Although the pre-specified analytical method to evaluate the null hypothesis will be the paired t-test, the Wilcoxon Signed-Rank test may be used as a sensitivity analysis if there is strong evidence the difference in LVOT VTI is not normally distributed.

Table 2: Power to Reject the Null Hypothesis for the Secondary Objective

Sample Size[1]	Statistical Method[2]	Power (%)
30	Paired t-test	83.3
	Wilcoxon Signed-Rank	80.5
35	Paired t-test	88.8
	Wilcoxon Signed-Rank	86.8
40	Paired t-test	92.6
	Wilcoxon Signed-Rank	91.3

[1]Number of subjects with paired LVOT VTI data available for analysis.
[2]Power for Wilcoxon Singed-Rank test based on the population LVOT VTI having an underlying normal distribution.

7.5.5.6 Determination of Subjects/Data for Analysis

All subjects with normal sinus node function and persistent 3rd degree AV block during Holter monitoring and with paired LVOT VTI measurements during MARVEL 2 adaptive pacing and VVI pacing will be included in the analysis. Note that as long as a subject's predominant rhythm can be determined from the Holter recording, the subject may be included in this analysis as determination of predominant rhythm does not require device marker channel.

For *de novo* subjects, only echocardiogram data collected at the pre-hospital discharge visit will contribute to the analysis of the secondary objective. However, if a *de novo* subject is missing paired

echocardiogram on the day following their Micra procedure but have paired LVOT VTI data from their 1-month visit, the 1-month data will be used in the analysis if available.

7.5.5.7 Missing Data and Sensitivity Analyses

Missing Data

Given the relatively short duration of the study, missing data is not expected to be a serious issue. However, missing data may arise if a subject does not perform the echocardiogram or the echocardiogram is uninterpretable by the echo core lab. Note that both reasons for missing data may plausibly be considered independent to change in LVOT VTI.

If the level of missing data is an issue, tipping point methodology will be employed to evaluate the sensitivity of the statistical inference to the missing data. Specifically, all subjects with missing data will be imputed to have the mean change and standard deviation in LVOT VTI in the observed data then iteratively set to a smaller mean change value until the statistical inference changes (i.e. P-value exceeds 0.05). Additionally, stochastic methods may be employed to aid in interpreting the likelihood the tipping point would be met or exceeded by determining how likely the mean value for subjects with missing data would exceed the tipping point.

Additional Sensitivity Analysis

Since *de novo* subjects may have more than one visit in which echocardiograms are obtained, the secondary objective will also be evaluated utilizing all available echocardiogram data. Specifically, a mixed effects linear regression model will be used to account for correlation in outcomes within subject to determine the effect of MARVEL 2 pacing on change in LVOT VTI. For this model, change in LVOT VTI will be the response and the model will incorporate an intercept and a random effect for subject. The fixed effects for the intercept term will be used to quantify the effect of MARVEL 2 adaptive pacing on LVOT VTI.

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7.7 Changes to Planned Analysis

Any deviation from the analyses described in the statistical analysis plan and a justification for making the change, will be described in the clinical study report.

8. References

[1]Ritter P, Duray, G, Zhang, S, et al. The rationale and design of the Micra Transcatheter Pacing Study: Safety and efficacy of a novel miniaturized pacemaker. Europace 2015; 17:807-813.

[2] Reynolds D, Duray GZ, Omar R, Soejima K, Neuzil P, Zhang S, Narasimhan C, Steinwender C, Brugada J, Lloyd M, Roberts PR, Sagi V, Hummel J, Bongiorni MG, Knops RE, Ellis CR, Gornick CC, Bernabei MA, Laager V, Stromberg K, Williams ER, Hudnall JH, Ritter P; Micra Transcatheter Pacing Study Group. A Leadless Intracardiac Transcatheter Pacing System. N Engl J Med. 2016 Feb 11;374(6):533-41.

[3]El-Chami MF, Al-Samadi F, Clementy N, Garweg C, Martinez-Sande JL, Piccini JP, Iacopino S, Lloyd M, Viñolas Prat X, Jacobsen MD, Ritter P, Johansen JB, Tondo C, Liu F, Fagan DH, Eakley AK, Roberts PR. Updated performance of the Micra transcatheter pacemaker in the real-world setting: A comparison to the investigational study and a transvenous historical control. Heart Rhythm 2018; 15(12): 1800-1807.

[4] Lloyd M, Reynolds D, Sheldon T, Stromberg K, Hudnall JH, Demmer WM, Omar R, Ritter P, Hummel J, Mont L, Steinwender C, Duray GZ. Rate adaptive pacing in an intracardiac pacemaker. Heart Rhythm. 2017 Feb;14(2):200-205

[5] Gillis AM, Russo AM, Ellenbogen KA, Swerdlow CD, Olshansky B, Al-Khatib SM, Beshai JF, McComb JM, Nielsen JC, Philpott JM, Shen WK. HRS/ACCF expert consensus statement on pacemaker device and mode selection. J Am Coll Cardiol. 2012 Aug 14;60(7):682-703.

[6] Chinitz L, Ritter P, Khelae SK, Iacopino S, Garweg C, Grazia-Bongiorni M, Neuzil P, Johansen JB, Mont L, Gonzalez E, Sagi V, Duray GZ, Clementy N, Sheldon T, Splett V, Stromberg K, Wood N, Steinwender C. Accelerometer-based atrioventricular synchronous pacing with a ventricular leadless pacemaker: Results from the Micra atrioventricular feasibility studies. Heart Rhythm. 2018 Sep;15(9):1363-1371.

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Summary of Changes

Version	Effective Date	Summary of Changes	Change Author
1.0	18 March 2019	Initial Release	