SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Implantable Cardiac Pacemaker (IPG)

Device Trade Name: Micra® Transcatheter Pacing System (Pacemaker Model MC1VR01 and Programmer Application Software Model SW022 Version 1.1)

Device Procode: PNJ

Applicant's Name and Address:
Medtronic, Incorporated
Cardiac Rhythm Disease Management
8200 Coral Sea Street NE
Mounds View, MN 55112

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number P150033

Date of FDA Notice of Approval: April 6, 2016

Priority Review: Granted priority review status on October 8, 2015 because the device represents a breakthrough technology.

II. INDICATION FOR USE

The Micra Transcatheter Pacing System is indicated for use in patients who have experienced one or more of the following conditions:

- symptomatic paroxysmal or permanent high-grade AV block in the presence of Atrial Fibrillation (AF)
- symptomatic paroxysmal or permanent high-grade AV block in the absence of AF, as an alternative to dual chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy
- symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses), as an alternative to atrial or dual chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy

Rate-responsive pacing is indicated to provide increased heart rate appropriate to increasing levels of activity.

III. CONTRAINDICATIONS

The Micra Model MC1VR01 pacemaker is contraindicated for patients who have the following types of devices implanted:

- An implanted device that would interfere with the implant of the Micra device in the judgment of the implanting physician
- An implanted inferior vena cava filter
- A mechanical tricuspid valve
- An implanted cardiac device providing active cardiac therapy which may interfere with the sensing performance of the Micra device

The device is contraindicated for patients who have the following conditions:

- Femoral venous anatomy unable to accommodate a 7.8 mm (23 French) introducer sheath or implant on the right side of the heart (for example, due to obstructions or severe tortuosity)
- Morbid obesity that prevents the implanted device to obtain telemetry communication within $\leq$12.5 cm (4.9 in)
- Known intolerance to the materials listed in "Section A.1, Physical characteristics" in the Clinician Manual, or heparin, or sensitivity to contrast medical which cannot be adequately premedicated

Steroid use – Do not use in patients for whom a single dose of 1.0 mg dexamethasone acetate cannot be tolerated.

For the MRI contraindications for patients with a Micra MRI device, refer to the Medtronic MRI Technical Manual.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Micra® Transcatheter Pacing System labeling.

V. DEVICE DESCRIPTION

The Medtronic Micra Model MC1VR01 single chamber implantable transcatheter pacing system (TPS) with SureScan technology is an MR Conditional programmable cardiac device that monitors and regulates the patient's heart rate by providing rate-responsive bradycardia pacing to the right ventricle.

The device senses the electrical activity of the patient's heart, using the sensing and pacing electrodes on the titanium capsule of the device. It monitors the heart rhythm for bradycardia and responds by providing pacing therapy based on the pacing parameters programmed. The device provides rate response, controlled through an activity based sensor. It also provides diagnostic and monitoring information for guidance in the pacing system evaluation and in patient care.

The Micra TPS consists of the implantable device that is a miniaturized single chamber (ventricular) pacemaker that will provide VVIR pacing therapy similar to currently marketed VVIR pacemaker systems, a transcatheter delivery system, and Programmer Software application (See Figure 1). The Micra device is a hermetically sealed self-contained pacemaker that is implanted directly into the right ventricle by a delivery catheter through the femoral vein. The system does not have transvenous leads and does not have a subcutaneous device pocket underneath the skin. The device is programmable to adjust both pacing and sensing operation to deliver right ventricular bipolar pacing and sensing. The delivery system is a steerable, non -over-the -wire (non-OTW) 23Fr (French) catheter delivery system. The Programmer Software Application Model SW022 supports all pacemaker features, including SureScan MRI, and is loaded on the commercially available Medtronic CareLink Programmer Model 2090. The Micra TPS utilizes commercially available standard pacemaker implant support instruments and accessories.

The Micra device contains an MCRD (Monolithic Controlled Release Device) which is a molded and cured mixture of dexamethasone acetate and liquid silicone rubber (LSR). The design intent of the MRCD is to deliver the steroid to reduce inflammation and fibrosis and is secured to the Cathode Electrode using medical adhesive. The target dosage of dexamethasone acetate in this device is 272 µg.

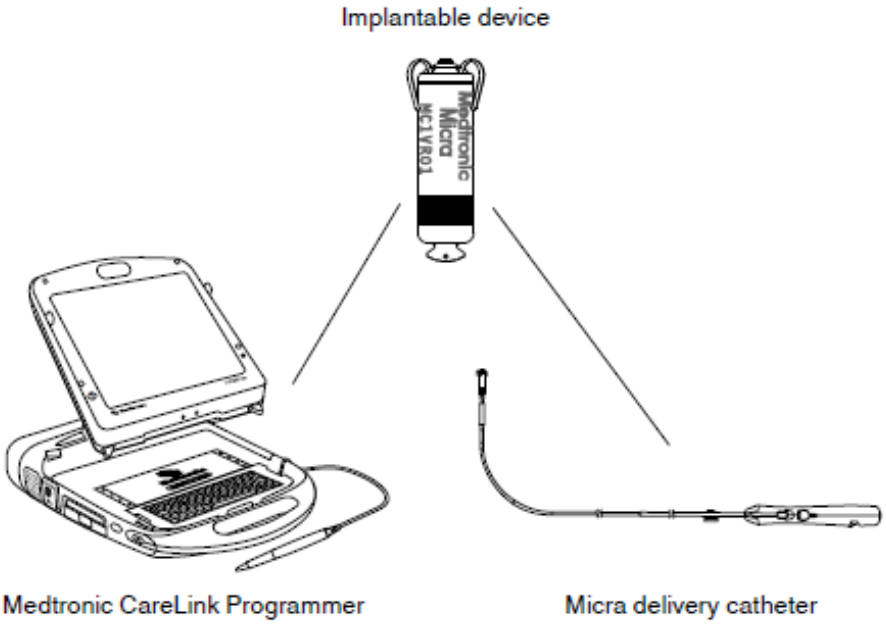


Figure 1: Micra Transcatheter Pacing System

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of bradycardia. Alternative therapies include the use of commercially available conventional pacemaker systems. Each system has its own advantages and disadvantages. A patient should fully discuss alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Micra TPS has been marketed commercially outside the United States since June, 2014. Specifically, the Micra TPS has been commercially distributed in the European Union, South Africa, Turkey, Israel, Saudi Arabia, and New Zealand. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Air embolism
- Aneurysm or pseudoaneurysm
- Bleeding or hematoma
- Cardiac or vascular trauma, such as cardiac perforation, dissection, rupture, or tear, possibly resulting in tamponade or arterio-venous fistula
- Device dislodgment or migration
- Device embolization
- Endocarditis
- Fluid accumulation
- General surgery risks and complications from comorbidities, such as hypotension,
- Dyspnea, syncope, pneumonia, hypertension, cardiac failure, renal failure, anemia, and death
- Heart, vessel, or valve tissue damage, including coronary arterial constriction
- Impaired cardiac function due to device
- Incision site complication such as excessive fibrotic tissue growth
- Incision site infection or other infection
- Induction or acceleration of arrhythmias, including heart block
- Ineffective rate response
- Myocardial damage
- Nerve damage
- Nerve or extra-cardiac stimulation
- Oversensing, undersensing, or loss of pacing therapy
- Pacemaker syndrome
- Pain at access site or chest
- Pericarditis, pericardia effusion, or pericardial rub
- Peripheral ischemia
- Reduced device longevity - results in device replacement procedure earlier than expected and could result in complications from replacement procedure
- Threshold elevation
- Thrombus which may result in embolism (for example, deep vein thrombosis, pulmonary embolism or cerebrovascular accident)

- Tissue necrosis such as myocardial infarction
- Toxic/allergic reactions, including body rejection phenomena and local tissue reaction
- Venous occlusion
- Vessel spasm

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

Nonclinical testing of the Micra TPS was conducted to ensure that the components and the finished device perform in accordance with their design specifications.

A. Laboratory Studies

Test	Acceptance Criteria	Results
Component and Subassembly Qualification Testing Specific components and subassemblies of the Micra Pacemaker were tested against their specific requirements. All of the components and subassemblies of the Micra TPS were qualified for use in the intended applications.		
Battery	59 samples Hermeticity helium leak rate $\leq 1 \times 10^{-8}$ cc/sec Voltage or no voltage across terminals	Passed
Electronic Module Assembly	22 samples	Passed
Additional Components/Subassemblies: Shield Insulator, Antenna Cup Assembly, Desiccant, Shields, Parylene Coating, Electrode Assembly, and Endcap Assembly		
Tines were tested for function, internal moisture and fixation. 10 samples were tested and conformed to specifications.		
Device Level Verification Testing This testing intended to verify the specified physical attributes of the implantable pacemaker.		
Electromagnetic Compatibility	This testing intended to verify that the device maintained appropriate functionality of intracardiac signal sensing with stresses imposed by radiation environments and to verify compliance to ISO 14708-2 and ISO 14117 and device labeling during testing with ambient electromagnetic fields inducing currents into the device.	
• Magnetic Field Electromagnetic Interference (EMI)	3 samples Verify appropriate signal sensing while device is exposed to magnetic fields.	Passed
• Radiated Immunity and Radio Compliance	3 samples Verify that commonly encountered modulated electromagnetic fields are unlikely to change the therapeutic behavior of the device.	Passed
• Non-Destructive EMI	3 samples Conform to Federal Communications Commission (FCC) regulations.	Passed

Test	**Acceptance Criteria**	**Results**
• Potentially Destructive EMI	22 samples Verify appropriate signal sensing while device is exposed to various sources of EMI	Passed
Mechanical Design Assurance Unit	All thermal and mechanical device environmental specification requirements were met. 22 samples are tested per specification and must result in the device remaining functional, components intact via visual/rattle check, no EIRs or patient safety deformations	
• Physical Dimensions	10 Samples Diameter 6.7mm ±0.2 Length 25.9 mm ±0.5 Length with Tines Unfolded max 34 mm Mass 1.75 grams ±0.5 Distance Between Electrodes 18 mm ±1.5 Anode Surface Area mm2 ±39 61 mm2	Passed
• Product ID and Shield Graphics	The device shield shall be labeled with the device family identifier graphic device therapy code, country of manufacture code, and serial number.	Passed
• Destructive Analysis	Performed on all failed devices.	N/A
• Barometric Pressure	Exposed to 60 cycles of high/low barometric pressure, simulating 100ft of seawater/mountain operation.	Passed
• Mechanical Shock	Subject to six 600G, 1ms mechanical shocks.	Passed
• Mechanical Vibration	Subject to random vibration for 30min on 3 perpendicular axes.	Passed
• Storage Temperature, temperature cycling. and temperature shock	Exposed to -35C for 48hrs, 58C for 48hrs and 70C for 2hrs. 5 cycles	Passed
• Disinfectant Exposure	Devices shall be free of construction and workmanship defects that would interfere with performance and reliability.	Passed
• Device Heat Generation	3 samples Device outer surface cannot be greater than 2°C above the surrounding body temperature of 37°C.	Non-compliant. Per ISO14708-1: Potential hazards assessment notes - device is within safe limits.
• Low Voltage Electrical Isolation	10 samples were confirmed to test that electrode sub-assembly design output meets the design input requirements. Measured impedances shall each exceed the input impedance of the hybrid for a frequency range of 0.1 to 100 kHz after being soaked in a 50 ohm-cm saline solution (NaCl) at 37 ±2 °C for 10 days minimum.	Passed
Electrical Design Verification Testing	All test results and analysis satisfy the final set of electrical requirements.	
• Accelerometer	Verify monotonicity, interface activity counts, signal bandwidth, output, and ADC offset.	
• Pacing	Verify device will detect rate limit violation, pacing output capacitance, discharge delay/duration, pulse characteristics, and pacing amplitudes.	

Test	Acceptance Criteria	Results
• Sensing	Verify sense amplifiers, common mode thresholds, accuracy of auto R and P wave measurements, and noise levels.	
• Telemetry	Verify fixed antenna coil inductance, programmer/device communication channel, bandwidth frequencies, and delays.	
• Memory	Verify procedure for flash memory requirements for read/write.	
• Current Drain	Measure current drain versus parameters for each device under test with single frequency, frequency modulated noise present, and while programmed to shipping parameters.	
• Capture Management	Verify functionality of ventricular capture management and performance with noise.	

Firmware
Firmware verification testing of the functionality and performance of the firmware against its firmware requirements demonstrated that all testable firmware requirements have been correctly implemented.

Software
Functional, installation, stress, and regression testing verified that all testable software requirements were correctly implemented and that the software requirements were met for Programmer Application Software Model SW022 (version 1.1).

Telemetry Security Testing
The Micra pacemaker communicates using Telemetry B. The system was tested and is in compliance to 47 CFR Part 15 requirements, compliance to standards related to EMC, as well as compliance to standards related to radio disturbance and immunity characteristics, including up to 10 volts/meter radiated immunity and no receiver exclusion band.

Sterilization
The Micra TPS sterilization process by 100% ethylene oxide (EO) was conducted in accordance with ISO 11135-1 and residuals were determined to be below acceptable limits per ISO 10993-7. These devices are intended for single use only, and will be labeled as 'STERILE'. Devices must have a sterility assurance of at least 10^{-6}.

Delivery System Verification Testing
This testing intended to verify the functional attributes of the delivery system including dimensional, safety, and performance to demonstrate that the Micra Delivery System meets all applicable performance specification requirements. The results demonstrated that the testing performed established acceptable functional performance.

Packaging
The system utilizes a primary (sterile package) and secondary packaging (shelf box) configuration. Package qualification testing was successfully completed to verify that the packaging protects the device and media during transportation and storage.

Shelf Life
The system's shelf life is based on battery capacity, package sterility, steroid stability, and delivery system integrity. Evidence provided for the Battery Capacity, Package Sterility, and Delivery System Integrity, as well as additional information pertaining to steroid stability supports a shelf life labeling of 9 months.

Biocompatibility
The Micra pacemaker and Micra Delivery Catheter have been evaluated for biological safety as guided by the applicable sections of ISO 10993-1:2009 and in compliance with ASTM/USP standards and guidelines. Results demonstrated that the system is biologically safe.

B. Animal Studies

A 12 week Good Laboratory Practice (GLP) study characterized the safety and performance of the device in 20 porcine subjects. The study evaluated the R-wave amplitude, lead impedance, pacing capture threshold, fixation performance, RF telemetry performance, and adverse events. The study confirmed the safety and performance of the device to be used in humans, with the limitation that the delivery of the device was via the jugular vein, not the femoral vein. The study concluded that one should pay attention to potential issues with cardiac perforation and myocardium thickness.

Prior to the GLP study, additional non-GLP and cadaver studies utilized 125 animals (canine, ovine, and porcine) plus 110 human hearts and cadavers to confirm design concepts and specifications. These studies included the following:

- Chronic Evaluation of the Micra System Safety and Performance
- Evaluation of Chronic R-Wave Behavior
- Delivery System Perforation Testing
- Rate Response Testing
- Chronic Extraction Study
- Effects of Induced Tine Fracture
- Tine Motion CT Imaging
- Micra Cardiac Anatomical Use Conditions
- Analysis of Cardiac Tissue Properties and Design of the Micra Fixation Mechanism
- Cadaver Testing
- 3D Proximity of Cardiac Landmarks to the skin in Humans
- Chronic Extraction Study
- Multiple Devices Implanted Studies

C. Additional Studies

1. Magnetic Resonance Imaging (MRI) Environment – Potential Hazards

The Micra pacemaker is labeled as MR Conditional under specified conditions.

The MRI-induced hazards for the Micra device were evaluated via bench testing, and the results of this assessment verify the Micra device functions as intended during and following exposure to the MRI environment.

The following mechanisms of potential MRI interactions with the Micra TPS due to exposure to magnetic fields were assessed: device heating, unintended cardiac stimulation, force, torque, vibration, and device malfunction. These interactions were evaluated by simulating the electrical and thermal properties of the human body in a coil exposed to clinical static/gradient/RF fields, injecting voltage pulses, and placing the device in MRI scanners to confirm relevant forces are within acceptable limits.

Clinical evaluation in humans was not completed because the firm has previously completed evaluations for the marketed Advisa MRI pacemaker, which was leveraged due to the reduced risk of MRI heating with the Micra device. This is due to the device design being smaller and lacking a cardiac lead, which acts as an antenna. Additionally, the bench test parameters implemented relevant clinical worst case exposures

2. System Verification and Validation Testing

System Verification testing focuses on verification of the functional attributes of the system against system requirements. System Validation testing consisted of evaluating the compatibility, interaction, and functional operation of the system components when used together as a system, which included the Micra device, along with programmers, accessory devices, application software, and manuals.

Based upon the systems testing conducted, the Micra device and the programmer application software model SW022 are validated for human use.

3. Human Factors and Usability

A Human Factors and Usability analysis was performed for the Micra TPS. The objective was to validate the Micra implant procedure, specifically the use of the delivery system for device implant and repositioning as well as to validate the design of new and modified functionality within the Micra Programmer user interface. This evaluation complied with EN 62366:2008 Medical Devices – Application of usability engineering to medical devices**.**

Additionally, representative intended users of the Programmer performed hypothetical but realistic clinical scenarios using the Medtronic CareLink Programmer model 2090 in the context of implant and follow-up care. Final results from the study indicate that the system can be implanted, repositioned, and programmed as intended as described in the Clinical Manual. The Micra TPS was determined acceptable for human use.

4. Risk Management

The Micra TPS development included a comprehensive risk management process conducted according to the principles of ISO 14971. The overall Micra system risk acceptability has been assessed by comparing Micra system potential risks to the well characterized risk profile of single chamber pacemaker systems. Comprehensive risk assessment concluded that the Micra system has risks mitigated as low as possible and that the residual risks are outweighed by the associated benefits.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Micra TPS for Class I or II indication for implantation of a single chamber ventricular pacemaker according to the ACC/AHA/HRS 2008 guidelines in the US under IDE G130245. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below. The clinical study was a global trial including investigational sites in Australia, China, India, Japan, Malaysia, South Africa, Czech Republic, Hungary, Republic of Serbia, Austria, Denmark, France, Greece, Italy, Netherlands, Spain, United Kingdom and Canada.

The Micra TPS IDE G130245 was a prospective, single-arm, multi-center clinical trial intended to evaluate the safety and effectiveness of the Micra TPS and to assess long-term device performance. The trial covered 56 investigational sites, which enrolled 744 patients, attempted 725 implants and resulted in 719 successfully implanted devices.

A. Study Design

Patients were treated between December 2013 and May 2015. The database for this PMA reflected data collected through June 24, 2015 and included 300 patients. There were 56 investigational sites.

The study was a prospective, single-arm, multi-center clinical study and implemented a group sequential analysis plan where the study's primary objectives could be evaluated at up to three (3) time points as described below. Per the Clinical Investigation Plan, study success would occur at the first analysis time point where the primary objectives were satisfied.

- The first interim analysis occurred when 300 implanted subjects were followed for at least 6-months post-implant and is the subject of this summary of safety and effectiveness.
- The second interim analysis, if needed, would have occurred when 450 implanted subjects have been followed for at least 6-months post-implant.
- The final analysis, if needed, would have occurred when 600 implanted subjects have been followed for at least 6-months post-implant.

The Hwang-Shih-DeCani alpha spending function with a gamma parameter of negative two (2) was used to control the overall alpha-level at 5% (two-sided; 2.5% one-sided) for each objective. For study success to occur, the null hypothesis needed to be rejected for both primary objectives at each objective's alpha level based on the alpha spending function. Based on the alpha spending rule the nominal alpha level at the first interim analysis was 0.0067 (i.e., p-value must be lower than 0.0067 for success) for the primary objectives.

Since the primary objectives of the study were met, secondary objectives #1 and #2 were tested using the Holm procedure to protect the overall type I error and allow statistically valid claims of significance.

The study continued as planned until all implanted subjects had an opportunity to complete the 12-month visit. Once all subjects had the opportunity to complete the 12-month follow-up visit, the study's long-term safety objective was evaluated. Clinical data were collected at baseline, implant/pre-hospital discharge, 1-month, 3-month, 6-month post-implant visits, and every 6 months thereafter until study closure.

The trial utilized a data monitoring committee (DMC) and a clinical events committee (CEC) as discussed below.

Clinical Events Committee

An independent CEC was established to review and adjudicate at a minimum all events classified by the investigator or Medtronic as procedure or system related to determine relatedness and major/minor complication or observation classifications. The CEC consisted of a minimum of three (3) non-Medtronic employed physicians who were not participating investigators for the study, including a CEC Chairperson.

Data Monitoring Committee

A DMC was established for assessing the accumulating data on safety of the therapy during the study. The DMC was responsible for safeguarding the interests of study subjects, assessing the safety of the Micra system during the study, and monitoring the overall conduct of the clinical study. To enhance the integrity of the study, the DMC also formulated recommendations related to the selection, recruitment, and retention of subjects, their management, improvement of adherence to protocol-specified regimens and procedures for data management and quality control. Additionally, the DMC was retained to evaluate the study results from the pre-specified interim analysis of the study's objectives.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the Micra TPS Global Clinical Trial study was limited to patients who met the following inclusion criteria:

Inclusion Criteria	
Criteria	**Rationale**
Subjects who have a Class I or II indication for implantation of a single chamber ventricular pacemaker according to ACC/AHA/HRS 2008 guidelines and any national guidelines[1,2]	Study will be evaluated in the standard patient population that is actually indicated for the device under evaluation.
Subjects who are able and willing to undergo the study requirements and are expected to be geographically stable for the duration of the follow-up.	Ensure ascertainment of data required for clinical evaluation.
Subjects who are at least 18 years of age (or older, if required by local law).	Ensure age is appropriate to provide informed consent.

Patients were not permitted to enroll in the Micra TPS Global Clinical Trial study if they met any of the exclusion criteria in the table below. There were two (2) phases for enrollment criteria regarding pacemaker dependent subjects:

- Phase 1: Initial enrollment was restricted to non-pacemaker dependent subjects (defined as escape rhythm ≤30 bpm).

- Phase 2: Restrictions against pacemaker dependent subjects were lifted after a steering committee safety review of the Holter and device diagnostic data from the 1st 25 usable Holters collected at the 1 month visit found that the device was performing as intended.

[1]Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. ACC/AHA/HRS 2008 Guidelines for Device-based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). 2008.

[2]Europace 2006 8. 746-837 doi:10.1093/europace/eul108

Exclusion Criteria	
Criteria	**Rationale**
Subjects who are entirely pacemaker dependent (escape rhythm ≤30 bpm). Note: Restrictions against pacemaker dependent patients were lifted on 7/23/2014 after a steering committee and data monitoring committee safety review of the Holter and device diagnostic data from the 1st 25 usable Holters at 1 month. FDA also reviewed the Holter analysis and provided permission to lift this exclusion criterion prior to informing study sites.	Subjects who are entirely pacemaker dependent will be excluded in the initial cohort until device reliability is verified in a conservative effort to maximize patient protection and minimize risk for potential patient harm.
Subject has an existing or prior pacemaker, ICD, or CRT device implant.	Avoid possible confounding factors (i.e., complications due to device change-outs).
Subject has unstable angina pectoris or has had an acute myocardial infarction (AMI) in the 30 days prior to eligibility assessment.	Avoid possible confounding factors (i.e., environment more susceptible to complications due to pre-existing conditions).
Subjects with current implantation of neurostimulator or any other *chronically* implanted device which uses current in the body. Note that a *temporary* pacing wire is allowed.	Necessary to avoid any possible electrical interference with Micra device.
Subjects with a mechanical tricuspid valve, implanted vena cava filter, or left ventricular assist device (LVAD).	Necessary to avoid electrical or mechanical interference when placing Micra device.
Subjects who are morbidly obese and physician believes telemetry communication of ≤5 inches (12.7 cm) could not be obtained with programmer head.	Necessary to ensure ability to communicate with programmer.
Subjects whose femoral venous anatomy is unable to accommodate a 23 French introducer sheath or implant on the right side of the heart (for example, due to obstructions or severe tortuosity) in the opinion of the implanter.	Necessary to place Micra introducer sheath.
Subjects who are considered as unable to tolerate an urgent sternotomy	Necessary in case of emergency where urgent vascular surgery would be required
Subjects with a known intolerance to Nickel-Titanium (Nitinol) Alloy.	Necessary since Micra tines are comprised of Nitinol material.
Subjects for whom a single dose of 1.0mg dexamethasone acetate may be contraindicated.	Necessary due to steroid material on Micra electrode (standard exclusion for all pacing studies with steroid on the electrode).

Exclusion Criteria	
Criteria	**Rationale**
Subjects with a life expectancy of less than 12-months.	Standard exclusion criteria to ensure study cohort is expected to survive to the time of endpoint evaluation.
Subjects who are currently enrolled or planning to participate in a potentially confounding drug or device trial during the course of this study. Co-enrollment in concurrent trials is only allowed when documented pre-approval is obtained from the Medtronic study manager.	Standard exclusion criteria to avoid confounding procedural requirements due to multiple experimental studies.
Pregnant women, or women of child bearing potential and who are not on a reliable form of birth control.	Standard exclusion criteria to avoid harm to the fetus caused by fluoroscopy requirements.
Subjects with exclusion criteria required by local law (e.g., age, breast feeding, etc.).	Standard exclusion criteria to comply with any additional local requirements which may apply.

2. Follow-up Schedule

   All patients were scheduled to return for follow-up examinations at pre-discharge, 1-month, 3-months, 6-months, and every six (6) months thereafter until study closure postoperatively.

   Data were collected using electronic case report forms (eCRFs) using an electronic data management system for clinical studies. In addition to eCRF data, non-CRF data was collected which included: digital medium for fluoroscopy cine recordings, x-rays, programmer strips, Holters, device interrogation files, and source documents (when requested).

   Preoperatively, patients were evaluated in accordance to the inclusion/exclusion criteria. Postoperatively, information from chest x-rays, electrical testing, rate response, and device interrogation were evaluated. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints: Safety

   The primary safety objective was to demonstrate that the freedom from major complications related to the Micra system and/or procedure at 6-months post-implant is greater than 83% (i.e., the lower boundary of the two-sided 95% confidence interval must be greater than 83%).

   Hypothesis

   H_o: S(6 months) $\leq$ 83%, versus

   H_a: S(6 months) > 83% where S(6-months) is the freedom rate at 6-months (183 days) post-implant for major complications related to the Micra system and/or procedure.

For an adverse event to meet the endpoint, the event must have occurred within 183 days (inclusive) of the Micra system implant and be adjudicated by the CEC as being a major complication related to the Micra system and/or procedure resulting in the following:

- Death
- Permanent loss of device function due to mechanical or electrical dysfunction of the device (e.g. pacing function disabled, leaving device abandoned electrically)
- Hospitalization
- Prolonged Hospitalization by at least 48 hours
- System revision (reposition, replacement, explant)

Performance Requirement
The lower boundary of the two-sided confidence interval for the freedom from major complications at 6-months (183 days) post implant related to the Micra system and/or procedure must be greater than 83% for the null hypothesis to be rejected. The null hypothesis could be rejected if the nominal P-value was less than 0.0067 at the first interim analysis. A sample size of up to 720 implanted provided more than 90% power to test the primary safety objective. A simulation study was performed to show that the empirical power to test the primary safety objective was approximately 92%.

Rationale for the Performance Requirement
The Micra system is analogous to a miniature single chamber pacemaker. Since Medtronic has not conducted a single chamber pacemaker study in recent years and contemporary evidence on the safety of single chamber pacing systems is limited, the performance requirement at 6-months post-implant was determined based on six (6) predicate studies of RV pacing leads and dual chamber pacing systems, as shown in Table 1. Estimates of the procedure and/or device related major complication rates 6-months post-implant were computed for the six (6) predicate studies by including only those major complications related to the IPG, RV lead, and/or procedure among those subjects with documented atrial fibrillation at baseline.

Table 1: Major System and Procedure Complication Freedom Rates for Computed[1] Single Chamber Pacemaker Studies (Subjects with AF)

Study	Study Description	Median Follow-up Months (IQR)	30-day Freedom Rate [n[2] at risk] (95% CI)	6-month Freedom Rate [n[2] at risk] (95% CI)
EnRhythm	Pre-market study evaluating the safety and clinical performance of the EnRhythm system	6.2 (5.9 – 7.1)	[58] 98.3% (88.8% - 99.8%)	[35] 96.6% (87.1% - 99.1%)
3830	IDE (G020043) study evaluating the safety and efficacy of the model 3830 lead[2,3]	25.8 (6.0 – 30.3)	[111] 91.2% (84.7% - 95.0%)	[87] 88.5% (81.4% - 93.0%)
5076	IDE (G990022) study comparing the safety and efficacy of the model 5076 lead to the 5068 lead[4]	11.7 (7.1 – 12.5)	[104] 94.8% (88.8% - 97.6%)	[91] 94.8% (88.8% - 97.6%)
EnRhythm MRI	IDE (G070056) study evaluating the safety and efficacy of the EnRhythm MRI in the MRI environment	29.7 (26.7 – 36.7)	[166] 89.3% (83.9% - 93.0%)	[161] 87.1% (81.4% - 91.2%)
Advisa MRI	IDE (G110046) study evaluating the safety and efficacy of the Advisa MRI in the MRI environment[5]	5.7 (3.9 – 6.9)	[74] 94.9% (86.9% - 98.5%)	[33] 93.6% (85.2% - 97.3%)
SAVEPACe	Post-market study comparing standard dual chamber and dual chamber minimal ventricular pacing algorithms[6]	23.6 (11.4 – 30.5)	[354] 93.9% (91.1% - 95.9%)	[311] 92.6% (89.5% - 94.8%)

[1]Computed single chamber rates obtained by excluding any adverse events that were only related to the right atrial lead from the analysis.

[2] n is the number of subjects reporting AF at baseline at risk for a major system and/or procedure related event.

[3]3830 (IDE G020043study used the randomized cohort from the 5076 study as an historical control.

[4]Includes data from 36 roll-in subjects, 59 non-roll-in subjects, 29 continued access subjects, and 2 subjects implanted but not meeting study's inclusion exclusion criteria.

[5]Includes data from 43 subjects randomized to model 5068 lead, 38 to subjects randomized to 5076 lead and 38 5076 roll-in subjects.

[5]Data presented based on PMA analysis cohort.

[6]SAVEPACe did not require follow-up of subjects with attempted but unsuccessful implants.

Demonstrating that the lower confidence boundary for the freedom rate from major complications related to the Micra system and/or procedure at 6-months post-implant is greater than 83% will ensure the Micra system has a safety profile compatible with current single chamber pacemaker technology when implanted in an analogous patient population. Prior to starting the study, Medtronic believed that the true freedom rate at 6-months post-implant for major complications related to the Micra system and/or procedure would be no lower than 90%, based on the 12.4% peri-procedural complication rate reported from a large registry study[3] of dual chamber and single chamber pacemakers as well as previous Medtronic studies. The lower confidence bound was set at 83% which is 7% lower than the lowest expected Micra rate to balance the number of subjects implanted with an investigational device while maintaining proof of acceptable performance.

Analysis Methods

A Kaplan-Meier survival analysis was conducted to estimate the freedom from adverse events classified as major complications that are related to the Micra system and/or procedure by the CEC within 6-months (183 days) post-implant. Days of follow-up for subjects successfully implanted with the Micra system were calculated as the minimum of the days from successful implant to: (1) onset date of a major complication related to the Micra system or procedure (if any), (2) study exit date (if exited), (3) death date (if death occurs), (4) last follow-up visit, or (5) 184 days.

The following subgroups were prospectively defined: sex, geography, and pacing dependence. The log-rank test was used to test for heterogeneity in major complication rates related to the Micra system and/or procedure between subgroups. All subjects with an attempted implant of the Micra system were included in the analysis.

Missing Data

Missing data occurred if a successfully implanted subject discontinued from the study (or died) without experiencing a major complication related to the Micra system and/or procedure prior to the 6-month visit. The reasons for the missing data were summarized to assess the plausibility that the missing data could change the statistical inference. The tipping point analysis iteratively imputed subjects censored prior to 6-months post-implant and prior to a Micra related major chronic complication as having a major chronic complication related to the Micra system and/or procedure in the order the subject was censored with subjects censored first imputed as having events first.

[3] Udo et al for the FOLLOWPACE Study. Heart Rhythm 2012;9:728 –735

4. Clinical Endpoints – Effectiveness

The primary effectiveness objective was to demonstrate the percentage of subjects with an adequate pacing capture threshold at 6-months post-implant exceeds 80% (i.e. the lower two-sided confidence interval must exceed 80%).

An adequate pacing capture threshold (PCT) is defined as:

1. A 6-month PCT $\leq$ 2V at a pulse duration of 0.24 ms AND
2. An increase in PCT from implant to 6-months $\leq$ 1.5 months (0.24 ms pulse width)

Hypothesis

H_o: $\pi \leq 80\%$, versus

H_a: $\pi > 80\%$ where π is the percentage of successfully implanted subjects with an adequate 6-month pacing capture threshold (PCT).

Performance Requirement

The lower boundary of the two-sided confidence interval for the percentage of subjects with an adequate 6-month pacing capture threshold must be greater than 80% for the null hypothesis to be rejected. The null hypothesis could be rejected if the nominal P-value is less than 0.0067 at the first interim analysis.

Rationale for the Performance Requirement

PCT as an effectiveness objective is a common electrical measure of pacing efficacy and is consistent with recent studies (e.g. 4195 and 4196 family of leads, EnRhythm MRI, Advisa MRI). A PCT requirement of 2 Volts at a pulse duration of 0.24 ms is a more rigorous requirement than PCT requirements for recent RV pacing/defibrillation leads evaluated by regulatory authorities when normalized to the same pulse duration. Micra utilizes different battery technology and nominally paces at a shorter pulse duration (0.24 ms vs 0.4 ms). Demonstrating that the PCT is less than 2 Volts for the vast majority of subjects will imply that the Micra system will have a longevity similar to current pacing systems since Micra's capture management feature will nominally set the safety margin to 0.5 Volts above the PCT with hourly confirmation of the PCT.

Analysis Methods

A manual (auto decrement) pacing threshold test was performed at implant and at the 6-month post-implant visit. For computing the percentage of subjects with an adequate 6-month PCT, all successfully implanted subjects with both an implant and 6-month visit were included with patients who had a system modification or alternate cardiac rhythm device implant with Micra turned off prior to the 6-month visit due to elevated pacing thresholds, or unable-to-capture at the 6-month visit due to a high PCT. The numerator was the number of subjects with a 6-month PCT less than or equal to 2 Volts who had an increase in PCT from implant to the 6-month visit of less than or equal to 1.5 Volts. Subject's unable-to-capture due to a high PCT at the 6-month visit was considered failures in the

analysis, along with subjects with a Micra system modification or alternate cardiac rhythm device implant with Micra turned off due to high thresholds prior to the 6-month visit were considered failures.

The following subgroups were prospectively defined: sex, geography, and pacing dependence. Fisher's exact test was used to test for heterogeneity in adequate 6-month PCT rates between subgroups.

Missing Data
Missing data occurred if a successfully implanted subject was discontinued from the study (or died) prior to the 6-month study visit, missed the 6-month visit, or a subject was missing their implant manual PCT test or 6-month visit manual PCT test. The reasons for the missing data were summarized to assess the plausibility that the missing data would change the statistical inference. Additionally, the following strategy was applied to evaluate the impact of the missing data:

1. Missing implant manual (auto decrement) PCT test: the missing manual PCT test was imputed with the automated capture management threshold test measured at implant if available, if not available the missing manual PCT test was imputed with the minimum weekly device measured PCT obtained from the device interrogation files within 14 days of implant.

2. Missing 6-month manual (auto decrement) PCT test: the missing manual PCT test was imputed with the automated capture management threshold test measured at the 6-month visit. If this value was not available, the missing manual PCT test was imputed with the maximum weekly device measured PCT obtained from the device interrogation files during the 6-month visit window. Note that since the minimum weekly device measured PCT is used for missing implant PCT and maximum weekly device measured PCT is used for missing 6-month PCT this imputation strategy is conservative since it will result in the largest change in PCT and highest 6-month PCT value.

3. For subjects where the endpoint remained missing after steps (1) and (2) (e.g,. exited or died prior to the six (6) month visit), a tipping point analysis was performed. Specifically, subjects with missing data were imputed as successes and then iteratively imputed as failures to identify the tipping point of the statistical test. In addition, for subjects included in the tipping point analysis the last available auto-decrement PCT test, last available capture management PCT test, and last available maximum weekly device recorded PCT test were listed to aid in the interpretation of the tipping point analysis.

   With regard to success/failure criteria, patient and study success are defined by meeting the above primary endpoints.

5. Secondary Objectives

Secondary Objective #1: Capture Management

The first secondary objective was to demonstrate the accuracy of Micra Ventricular Capture Management (VCM) pacing thresholds compared to manual pacing capture thresholds.

This objective was evaluated by demonstrating the percentage of subjects successfully implanted with the Micra system who have a VCM pacing threshold within 0.5V of the PCT measured manually (at a pulse duration of 0.24 ms) exceeds 85% (i.e. the lower boundary of the two-sided confidence interval must exceed 85%).

Hypothesis

H_o: $\pi \leq 85\%$, versus

H_a: $\pi > 85\%$ where π is the percentage of subjects that have a VCMT that is within 0.5 Volts of the manual (auto decrement) PCT (0.24 ms pulse width) at the 6-month post-implant visit.

Performance Requirement

To reject the null hypothesis, the Holm procedure adjusted p-value must be less than the alpha level dictated by the alpha spending function. Rejection of the null hypothesis implies that the lower boundary of the two-sided confidence interval for the percentage of subjects with a VCMT within 0.5 Volts of the manual PCT (0.24 ms pulse width) at the 6-month post-implant visit will be greater than 85%. The null hypothesis could be rejected if the Holm adjusted P-value is less than 0.0067 at the first interim analysis.

Analysis Methods

A manual (auto decrement) pacing threshold test was performed at the implant, 3-month, and 6-month follow-up visit. Additionally, a VCMT test was performed in the study clinic at implant and each scheduled follow-up visit. Values from the manual PCT test and VCMT test were recorded on the eCRFs. For computing the percentage of subjects with a VCMT that is within 0.5 Volts of the manual PCT (0.24 ms pulse width), total subjects included those with a valid manual PCT test and VCMT test performed at 0.24 ms at the 6-month post-implant visit. The numerator was all subjects in the denominator with a VCMT that was within 0.5 Volts (±0.5 Volts inclusive) of the manual PCT. Subjects where one of the tests (VCMT or manual PCT) fails to capture were included as failures in the analysis.

Missing Data

Missing data occurred if a successfully implanted subject discontinued from the study or died prior to the 6-month study visit, missed the 6-month visit, or a subject was missing a valid manual (auto decrement) PCT test or VCMT at the 6-month visit. The following strategy was applied to evaluate the impact of the missing data:

1. Missing VCMT test only: impute the missing in-office VCMT test with the closest valid PCT obtained from the automated VCMT and stored in device memory provided the closest device measured PCT occurs within 14 days of the 6-month visit; otherwise if still missing, impute with the in-office VCMT from the 3-month visit.

2. Missing manual (auto decrement) PCT only: impute with the manual PCT recorded at the 3-month visit.

3. Missing both VCMT and manual PCT: impute with VCMT and manual PCT from the 3-month visit.

4. For subjects where the endpoint remains missing, a tipping point analysis was performed.

5. Specifically, subjects with missing data were imputed as successes and then iteratively imputed as failures to identify the tipping point of the statistical test.

Secondary Objective #2: Rate Response
The second secondary objective was to demonstrate the rate response operation of the Micra system.

This objective was assessed by determining if the Micra sensor-indicated rate derived from the input of the accelerometer during the Minnesota Pacemaker Response Exercise Protocol (M-PREP) was proportional to the workload using the Kay-Wilkoff model. This objective was evaluated in a subset of study sites at the 3-month and 6-month visits.

Hypothesis
H_o: $\beta kw < 0.65$ or $\beta kw > 1.35$, versus
H_a: $0.65 \leq \beta kw \leq 1.35$ where βkw is the mean slope parameter from the Kay-Wilkoff model.

Performance Requirement
The Two (2) One-sided Test (TOST) procedure for establishing equivalence must reject the null hypothesis at the 0.05 level. The Holm adjusted p-value for testing this hypothesis was computed from the maximum p-value associated with each one-sided test. If the Holm adjusted p-value was less than 0.05 then the null hypothesis could be rejected implying the Kay-Wilkoff slope parameter is close to one. Rejecting the null hypothesis implies that the two-sided 90% confidence interval will lie within the interval of 0.65 and 1.35 and indicate that the Micra system provides adequate rate response operation.

Analysis Methods

Information regarding the M-PREP test was collected on the eCRF at the 3-month and 6-month visit. The device memory stored the sensor-indicated rate. The sensor-indicated rate and workload (in METS) were normalized for each subject following method 1 of Kay (1992)[4]. Specifically, the normalized sensor rate was computed for each M-PREP stage as:

$$\text{normalized sensor rate} = \frac{(\text{sensor rate at stage} - \text{sensor rate at rest})}{(\text{maximum sensor rate} - \text{sensor rate at rest})}$$

Likewise the normalized workload was computed for each M-PREP stage as:

$$\text{normalized workload} = \frac{(\text{METS at stage} - 1)}{(\text{maximum METS} - 1)}$$

A random effects linear regression model that allowed for subject specific intercepts, slopes, and slope by visit interaction and fixed effect for study visit was the pre-specified method for estimation of the population slope (β_{KW}) and its standard error. Only data from visits in which the subject completed at least stage 4 of the M-PREP protocol were included in the analysis.

Missing Data

The rate response feature cannot be adequately tested unless subjects reach at least stage 4 of the M-PREP test and do not continuously use the treadmill handlebars. Therefore, missing data is not an issue for the evaluation of this objective.

6. Ancillary Objectives

The following ancillary objectives were descriptive without established performance requirements or statistical hypotheses.

a. Summarize Micra longevity estimates at 6-months
b. Summarize adverse events
c. To characterize electrical performance (pacing impedance and sensing amplitude) of the Micra system
d. To characterize the implant procedure including
   Implant success rate
   Total implant time
   - Changes to anticoagulation medications
   - Fluoroscopy time
   - Number of tines engaged
   - Number of days in hospital for implant
e. Summarize Micra performance via ambulatory Holter monitoring findings

[4] Kay, GN. 1992. Quantitation of chronotropic response: comparison of methods for rate-modulating permanent pacemakers. JACC 20 (7) 1533 – 1541.

f. Summarize quality of life
g. Summarize changes in device orientation

B. Accountability of PMA Cohort

At the time of database lock, a total of 744 subjects were enrolled at 56 centers in 19 countries worldwide. There were 725 subjects who had a Micra implant attempt with 719 subjects successfully implanted with the Micra system. There were 6 subjects with a Micra implant attempt that were not successfully implanted with a Micra system; 5 of the 6 received an alternate system. Figure 2 displays the disposition of all 744 enrolled subjects.

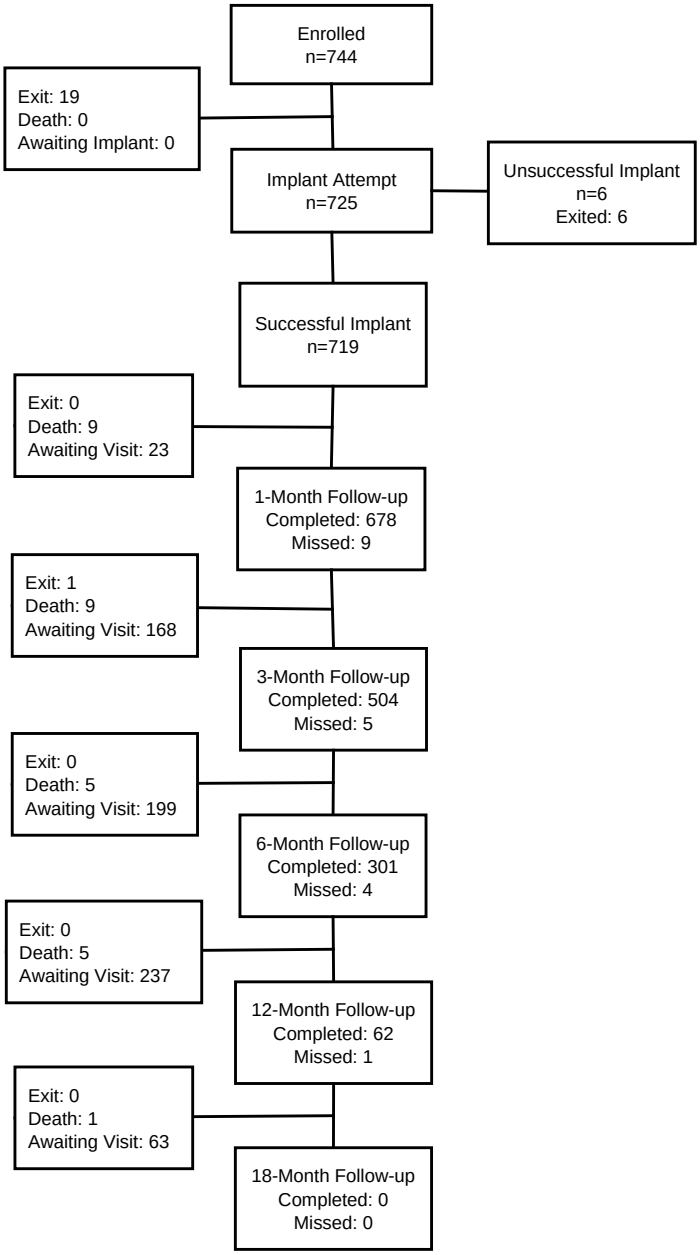


Figure 2: Patient Disposition

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a single chamber pacemaker prospective study performed in the US. As shown in Table 2, of the 744 enrolled subjects, 309 (42%) were female and the average age was 76 years. The Micra study cohort reflects a broad exposure across numerous countries and ethnicities, with a variety of implanted subjects:

- average weight 79 kg/174 lbs. (ranging from 37-155 kg/82-342 lbs.)
- average height 169 cm/66.5 in. (ranging from 134-203 cm/52.8-79.9 in.)
- average BMI 27.6 (ranging from 14-57)
- average age 76 years (ranging from 19-94 years)
- average LVEF 58.8 ± 8.8 (ranging from 25-91%)

Table 2: Baseline Demographics

Subject Characteristics	Enrolled (N = 744)	Implanted (N = 719)
Gender (N,%)		
Male	434 (58.3%)	424 (59.0%)
Female	309 (41.5%)	295 (41.0%)
No response	1 (0.1%)	0 (0.0%)
Age (years)		
Mean ± Standard Deviation	75.7 ± 11.0	75.8 ± 11.0
Median	78.0	78.0
25^{th} Percentile - 75^{th} Percentile	71 - 83	72 - 83
Minimum – Maximum	19 - 94	19 - 94
Subjects With Measure Available (N,%)	743 (99.9%)	719 (100.0%)
Race (N,%)*		
Not reportable per local laws or regulations	181 (24.3%)	179 (24.9%)
Subject/physician chose not to provide information	2 (0.3%)	2 (0.3%)
White or Caucasian	447 (60.1%)	431 (59.9%)
Black	21 (2.8%)	20 (2.8%)
Asian Indian	23 (3.1%)	23 (3.2%)
Chinese	15 (2.0%)	13 (1.8%)
Japanese	38 (5.1%)	36 (5.0%)
Other Asian	12 (1.6%)	12 (1.7%)
Two or more races	4 (0.5%)	3 (0.4%)
No response	1 (0.1%)	0 (0.0%)
Ethnicity (N,%)*		
Not reportable per local laws or regulations	185 (24.9%)	182 (25.3%)
Subject/physician chose not to provide information	8 (1.1%)	6 (0.8%)
Not Hispanic or Latino	464 (62.4%)	446 (62.0%)
Hispanic or Latino	14 (1.9%)	13 (1.8%)
No response	73 (9.8%)	72 (10.0%)

*Regulation in many European Union countries preclude the collection of race, and therefore this could not be collected, so it is not possible to accurately determine the percentage of non-white/non-Caucasian subjects.

Table 3 summarizes the primary pacing indication for the 744 enrolled subjects and indicates that 64% of the 719 successfully implanted subjects had a pacing indication associated with persistent or permanent atrial arrhythmias. The proportion of subjects (baseline demographics) who had any atrial fibrillation was 72.6%, and 27.4% did not have a history of AF. Among those 27.4% (n=199) without AF, 16.1% (n=32) had a primary indication of sinus bradycardia and 3.5% (n=7) had a primary indication of tachycardia-bradycardia.

Additionally, 2.8% subjects successfully implanted with the Micra system were considered pacemaker dependent (escape rhythm ≤30 bpm) at the time of their Micra implant.

Table 3: Primary Pacing Indication

Subject Characteristics	Enrolled (N = 744)	Implanted (N = 719)
Symptomatic Sinus Node Dysfunction	**323 (43.4%)**	**310 (43.1%)**
Without AV Block and without persistent/permanent atrial arrhythmias	118 (15.9%)	114 (15.9%)
With AV Block and with persistent/permanent atrial arrhythmias	41 (5.5%)	40 (5.6%)
With AV Block but without persistent/permanent atrial arrhythmias	12 (1.6%)	12 (1.7%)
Without AV Block but with persistent/permanent atrial arrhythmias	152 (20.4%)	144 (20.0%)
AV Blocks	**361 (48.5%)**	**351 (48.8%)**
2nd degree without atrial arrhythmias	45 (6.0%)	44 (6.1%)
3rd degree without atrial arrhythmias	67 (9.0%)	62 (8.6%)
AV block with atrial arrhythmias	186 (25.0%)	184 (25.6%)
Pending AV nodal ablation with atrial arrhythmias	62 (8.3%)	61 (8.5%)
Pending AV nodal ablation without atrial arrhythmias	1 (0.1%)	0 (0.0%)
Other Indications	**59 (7.9%)**	**58 (8.1%)**
Syncope	17 (2.3%)	16 (2.2%)
Other with atrial arrhythmias	31 (4.2%)	31 (4.3%)[1]
Other without atrial arrhythmias	11 (1.5%)	11 (1.5%)[2]
No Response	1 (0.1%)	0 (0.0%)
Pacing Indications Associated with pers/perm atrial arrhythmias (N, %)		
Yes	472 (63.4%)	460 (64.0%)
No	271 (36.4%)	259 (36.0%)
Escape Rhythm ≤30 bpm (N, %)		
Yes	20 (2.7%)	20 (2.8%)
No	721 (96.9%)	699 (97.2%)
No response	3 (0.4%)	0 (0.0%)

Subject Characteristics	Enrolled (N = 744)	Implanted (N = 719)

[1]Includes drug induced bradycardia (6), carotid sinus syndrome (11), atrial fibrillation with bradycardia (6), atrial fibrillation with long R-R intervals (3), atrial flutter with long R-R interval (1), intrinsic conduction system disease (1), permanent atrial fibrillation with intermittent pauses (1), persistent junctional rhythm after TAVI (1), and underlying bifasicular block (1).

[2]Includes carotid sinus syndrome (2), left bundle branch block (3), trifasicular block (3), swallow syncope (1), bifasicular block (1), and conduction disorder infrahisian (HV=80) (1).

Table 4 indicates that the most frequent reason for implanting a single chamber pacemaker among the 744 enrolled subjects was indication(s) associated with persistent/permanent/chronic atrial tachycardia/fibrillation flutter (65%) followed by frequent pacing not expected (30%).

Tables 5-7 illustrate common medical history reported in the clinical study. The most commonly reported medical history was hypertension followed by supraventricular tachyarrhythmias with 78% and 75% of enrolled subjects reporting respectively. Of note, 13% of enrolled subjects reported a history of COPD and 11% of enrolled subjects reported a history of pulmonary hypertension. The most common cardiovascular medications used at baseline were ACE inhibitors (49%), followed by anticoagulants (45%) and diuretics (32%).

Table 4: Atrial Arrhythmia History

Subject Characteristics (N, %)	Enrolled (N = 744)	Implanted (N = 719)
Atrial arrhythmias, NONE	171 (23.0%)	165 (22.9%)
AV nodal re-entrant tachycardia	4 (0.5%)	3 (0.4%)
Premature atrial complexes	49 (6.6%)	47 (6.5%)
Premature atrial complexes, non-conducted	2 (0.3%)	2 (0.3%)
SA nodal re-entry	0 (0.0%)	0 (0.0%)
Supraventricular tachycardia	559 (75.1%)	543 (75.5%)
Atrial fibrillation, paroxysmal	133 (17.9%)	126 (17.5%)
Atrial fibrillation, persistent	145 (19.5%)	138 (19.2%)
Atrial fibrillation, permanent	277 (37.2%)	274 (38.1%)

Subject Characteristics (N, %)	Enrolled (N = 744)	Implanted (N = 719)
Atrial flutter	111 (14.9%)	107 (14.9%)
Atrial tachycardia	33 (4.4%)	30 (4.2%)
Wandering atrial pacemaker	0 (0.0%)	0 (0.0%)
Other atrial arrhythmias	6 (0.8%)	4 (0.6%)
No response	3 (0.4%)	0 (0.0%)

Table 5: Sinus Node Dysfunction History

Subject Characteristics (N, %)	Enrolled (N = 744)	Implanted (N = 719)
Sinus Node Dysfunction, NONE	367 (49.3%)	360 (50.1%)
Bradycardia - tachycardia syndrome	175 (23.5%)	167 (23.2%)
Chronotropic incompetence	23 (3.1%)	23 (3.2%)
Sinus arrest / pause / exit block	133 (17.9%)	127 (17.7%)
Sinus bradycardia	139 (18.7%)	135 (18.8%)
Sinus tachycardia	12 (1.6%)	11 (1.5%)
Other sinus node dysfunction	7 (0.9%)	6 (0.8%)
No response	3 (0.4%)	0 (0.0%)

Table 6: Ventricular Arrhythmia History

Subject Characteristics (N, %)	Enrolled (N = 744)	Implanted (N = 719)
Ventricular arrhythmias, NONE	588 (79.0%)	569 (79.1%)
Premature ventricular complexes	130 (17.5%)	127 (17.7%)
Torsades de pointes	3 (0.4%)	3 (0.4%)
Ventricular fibrillation	2 (0.3%)	2 (0.3%)
Ventricular flutter	1 (0.1%)	1 (0.1%)
Ventricular tachycardia, non-sustained	38 (5.1%)	38 (5.3%)
Ventricular tachycardia, sustained monomorphic	0 (0.0%)	0 (0.0%)
Ventricular tachycardia, sustained polymorphic	1 (0.1%)	1 (0.1%)
Ventricular tachycardia, sustained, unknown morphology	0 (0.0%)	0 (0.0%)

Subject Characteristics (N, %)	Enrolled (N = 744)	Implanted (N = 719)
Other ventricular arrhythmias	7 (0.9%)	7 (1.0%)
No response	3 (0.4%)	0 (0.0%)

Table 7: AV Junctional Arrhythmia and Block History

Subject Characteristics (N, %)	Enrolled (N = 744)	Implanted (N = 719)
AV junctional arrhythmias and blocks, NONE	326 (43.8%)	317 (44.1%)
1st degree AV block	89 (12.0%)	85 (11.8%)
2nd degree AV block	83 (11.2%)	82 (11.4%)
3rd degree AV block	144 (19.4%)	140 (19.5%)
AV junctional rhythm	31 (4.2%)	31 (4.3%)
Left bundle branch block	98 (13.2%)	98 (13.6%)
Intraventricular conduction delay	8 (1.1%)	7 (1.0%)
Right bundle branch block	131 (17.6%)	129 (17.9%)
Pre-excitation syndromes (e.g. Wolf Parkinson White)	0 (0.0%)	0 (0.0%)
Premature junctional contractions	1 (0.1%)	1 (0.1%)
Other AV junctional arrhythmias and blocks	63 (8.5%)	59 (8.2%)
No response	3 (0.4%)	0 (0.0%)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the treated cohort of 300 patients/procedures, etc. available for the 6-month evaluation. The 300th 6-month follow-up visit was completed on May 19, 2015 triggering the visit cutoff for the data reported in this summary (note that there were 301 6-month visits accrued by this date). At the time of the visit cutoff, 725 subjects had an attempted implant of the Micra system and were included in the analysis. The key safety outcomes for this study are presented below. Clinical review indicates that the new delivery system and fixation method warrant additional attention for vascular access and cardiac injuries and resulting interventions.

Adverse effects that occurred in the PMA clinical study:

There were 609 adverse events reported by 338 (46.6%) of the 725 subjects with an attempted implant. Of the 609 adverse events, 601 occurred during or following a Micra implant attempt; 54 in 48 subjects were considered system or procedure related complications and 28 in 25 subjects were considered system or procedure related major complications and met the primary safety endpoint. A

summary of all reported system and procedure related complications is shown in Table 8. Of the 28 major complications, the majority (54%) occurred within 1 day of a Micra implant attempt, with 71% within 7 days of an implant attempt. All major complications have occurred within 6-months of the implant attempt.

Table 8: System or Procedure Related Complications

	No. Events (No. Subjects, %)	
Adverse Event Key term	**All Complications**	**Major Complications**
Total Events	**54 (48, 6.62%)**	**28 (25, 3.45%)**
Cardiac Arrhythmias	**7 (7, 0.97%)**	**0 (0, 0%)**
Atrioventricular Block Complete	5 (5, 0.69%)	0 (0, 0%)
Ventricular Fibrillation	1 (1, 0.14%)	0 (0, 0%)
Ventricular Tachycardia	1 (1, 0.14%)	0 (0, 0%)
Embolism and Thrombosis	**3 (3, 0.41%)**	**2 (2, 0.28%)**
Deep Vein Thrombosis	2 (2, 0.28%)	1 (1, 0.14%)
Pulmonary Embolism	1 (1, 0.14%)	1 (1, 0.14%)
Events at Groin Puncture Site	**11 (11, 1.52%)**	**5 (5, 0.69%)**
Arterial Injury	1 (1, 0.14%)	0 (0, 0%)
Arteriovenous Fistula	4 (4, 0.55%)	4 (4, 0.55%)
Incision Site Haematoma	1 (1, 0.14%)	0 (0, 0%)
Incision Site Haemorrhage	2 (2, 0.28%)	0 (0, 0%)
Incisional Drainage	2 (2, 0.28%)	0 (0, 0%)
Vascular Pseudoaneurysm	1 (1, 0.14%)	1 (1, 0.14%)
Traumatic Cardiac Injury	**12 (12, 1.66%)**	**11 (11, 1.52%)**
Cardiac Perforation	3 (3, 0.41%)	3 (3, 0.41%)
Pericardial Effusion	9 (9, 1.24%)	8 (8, 1.10%)
Pacing Issues	**2 (2, 0.28%)**	**2 (2, 0.28%)**
Device Dislocation	1 (1, 0.14%)[1]	1 (1, 0.14%)
Device Pacing Issue	1 (1, 0.14%)	1 (1, 0.14%)
Other	**19 (19, 2.62%)**	**8 (8, 1.10%)**
Acute Myocardial Infarction	1 (1, 0.14%)	1 (1, 0.14%)
Cardiac Failure	3 (3, 0.41%)	3 (3, 0.41%)
Hypotension	3 (3, 0.41%)	0 (0, 0%)
Medication Error	2 (2, 0.28%)	0 (0, 0%)
Metabolic Acidosis	1 (1, 0.14%)	1 (1, 0.14%)
Non-Cardiac Chest Pain	1 (1, 0.14%)	0 (0, 0%)
Osteoarthritis	1 (1, 0.14%)	0 (0, 0%)
Pacemaker Syndrome	1 (1, 0.14%)	1 (1, 0.14%)
Pericarditis	1 (1, 0.14%)	0 (0, 0%)
Presyncope	3 (3, 0.41%)	1 (1, 0.14%)
Syncope	1 (1, 0.14%)	1 (1, 0.14%)

	No. Events (No. Subjects, %)	
Adverse Event Key term	**All Complications**	**Major Complications**
Urinary Retention	1 (1, 0.14%)	0 (0, 0%)

[1]Increased pacing capture threshold described as micro-dislodgement by investigator. Chest X-ray showed device was in place.

The most common reason an event met the major complication endpoint was prolonged hospitalization (18 of 28 or 64% of major complications) as displayed in Table 9. Of the 725 subjects with an implant attempt, 3 (0.4%) required a system revision. Only 1 major complication resulted in a subject death. Of the 29 reported deaths, there were no device related deaths adjudicated by the CEC and only 1 procedure related death.

Table 9: Major Complication Criteria Met (Including Deaths)

Major Complication Criterion (not Mutually Exclusive)	Major Complications (N = 28)
Led to death	1 (3.6%)
Led to permanent loss of device function due to mechanical or electrical dysfunction of the device	1 (3.6%)
Led to hospitalization	13 (46.4%)
Led to prolonged Hospitalization by 48 hours or more	18 (64.3%)
Led to system revision (explant, reposition, replacement)	3 (10.7%)

Tables 10 and 11 on cardiac and vascular injury compare events reported due to the initial system implant among the clinical study, continued access study, Advisa MRI study, and historical control. Advisa is an appropriate comparator given it was a recent study completed in 2012 and the system is the only single chamber pacemaker with similar MRI compatibility. The resulting interventions due to cardiac injury indicate the need for careful labeling and consideration when selecting a patient and performing the implant procedure.

Table 10: Perforation and Effusion

	Micra IDE (n=725) (n=13 total events, 12 complications, 11 major complications)	Micra Continued Access (n=56) (n=2 total events, 2 major complications	Advisa MRI (n=266) (n=9 total events, 8 complications, 7 major complications)	Full Historical Control (n=2667) (n=50 total events, 32 major complications, 7 minor complications)
Hypotension	54% (7 of 13)	50% (1 of 2)	11% (1 of 9)	24% (12 of 50)
Shock/Tamponade	31% (4 of 13)	50% (1 of 2)	0% (0 of 9)	16% (8 of 50)
CPR	15% (2 of 13)	0% (0 of 2)	0% (0 of 9)	0% (0 of 50)
Intubation	8% (1 of 13)	50% (1 of 2)	0% (0 of 9)	0% (0 of 50)

Prolonged or New Hospitalization	85% (11 of 13)	100% (2 of 2)	100% (9 of 9)	54% (27 of 50)
Pericardiocentesis	70% (9 of 13)	50% (1 of 2)	11% (1 of 9)	22% (11 of 50)
Surgical Repair	15% (2 of 13)	50% (1 of 2)	0% (0 of 9)	4% (2 of 50)
Lead Revision	Not applicable	Not applicable	44% (4 of 9)	24% (12 of 50)
Resulted in death	0% (0 of 13)	0% (0 of 2)	0% (0 of 9)	0% (0 of 50)

*Not mutually exclusive; a single event may apply to multiple symptoms or interventions

Table 11: Vascular Injury

	Micra IDE (n=725) =AV fistula, arterial injury, pseudoaneurysm (n=12 total, 6 complications, 5 major complications)	Micra Continued Access (n=56) =AV fistula, arterial injury, pseudoaneurysm (n=1, 1 major complication)	Advisa MRI (n=266) Vascular Injury (n=0)	Full Historical Control (n=2667) (n=1 total event)
Hypotension	0	0	0	0
Shock/Tamponade	0	0	0	0
CPR	0	0	0	0
Intubation	0	0	0	0
Prolonged or New Hospitalization	5	1	0	1
Pericardiocentesis	0	0	0	0
Surgical Intervention/Repair	4	0	0	0
Resulted in death	0	0	0	0
Other	3	0	0	0

*Not mutually exclusive; a single event may apply to multiple symptoms or interventions

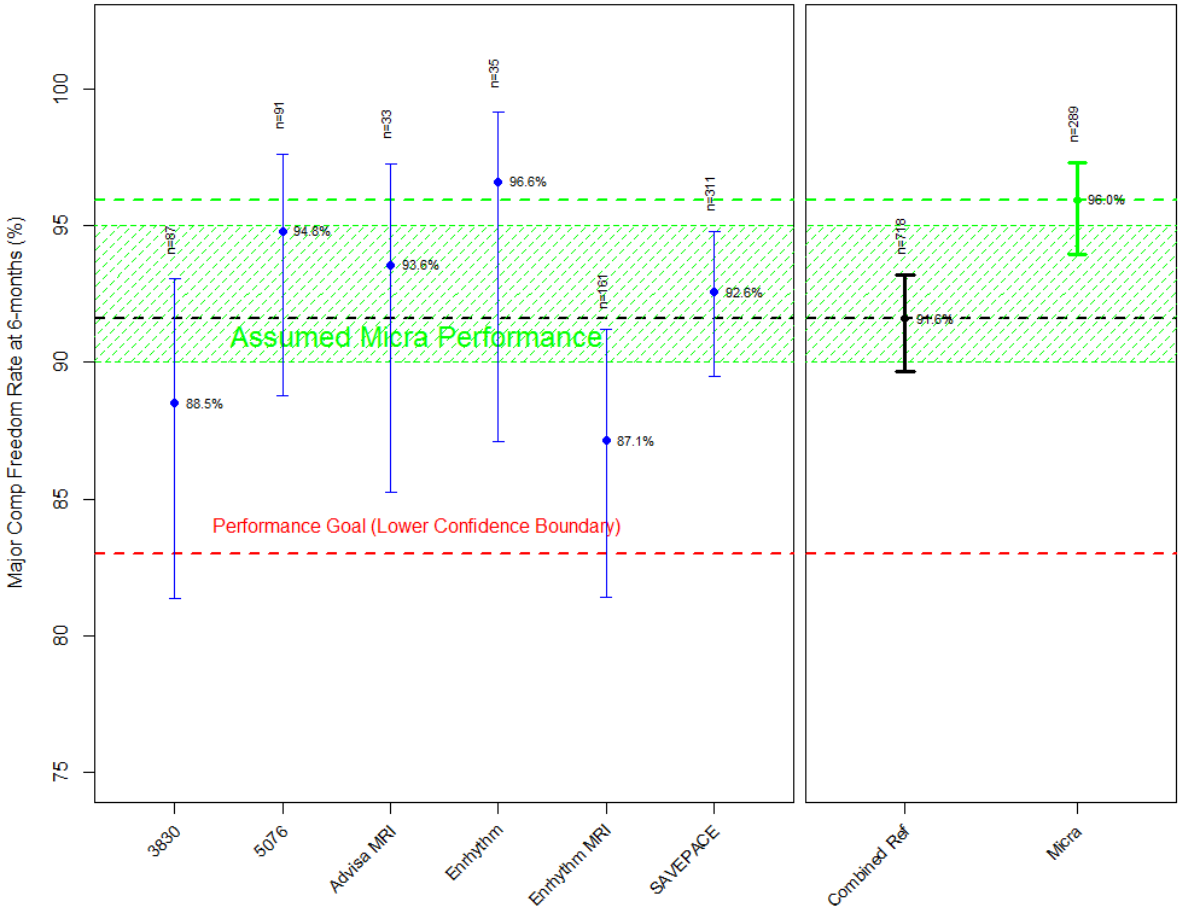
The Kaplan-Meier estimate for the freedom from major complications related to Micra system or procedure at 6-months (183 days) post-implant was 96.0% (98.66% CI: 93.3% - 97.6%). This was higher than the pre-specified performance criterion of 83% (P<0.0001). Since the p-value associated with this test was lower than the p-value required to reject the null hypothesis at the first interim analysis (0.0067), the null hypothesis was rejected and the primary safety objective was considered met.

There are 387 implanted subjects who have not had a major complication and have not yet completed at least 183 days of follow-up. These 387 subjects along with all other subjects active in the Micra study continue to be followed to complete the 12-month follow-up visit. Thus far, there has been no change in the estimated major complication rate between 6 and 12 months.

The 6-month freedom from major complications rate for the 6 pacemaker studies in Table 1 (n=977 implant attempts with n=718 subjects at risk at 6-months post-implant) was 91.6% with a 95% confidence interval of 89.7% - 93.2%. In comparison, the 6-month freedom from major complication rate for Micra was 96.0% with a 98.66% confidence interval of 93.3% to 97.6%. The 977 subjects refer to the group which represents the single chamber data set. Figure 3 shows

the individual complication free rates and confidence boundaries of the referenced studies in comparison to Micra. This suggests that the Micra safety profile is clinically acceptable compared to the predicate pacing systems.

Figure 3: 6-Month Freedom from Major Procedure or System Related Complications (Micra vs Reference Dataset – 977 AF Reference Subjects Only)



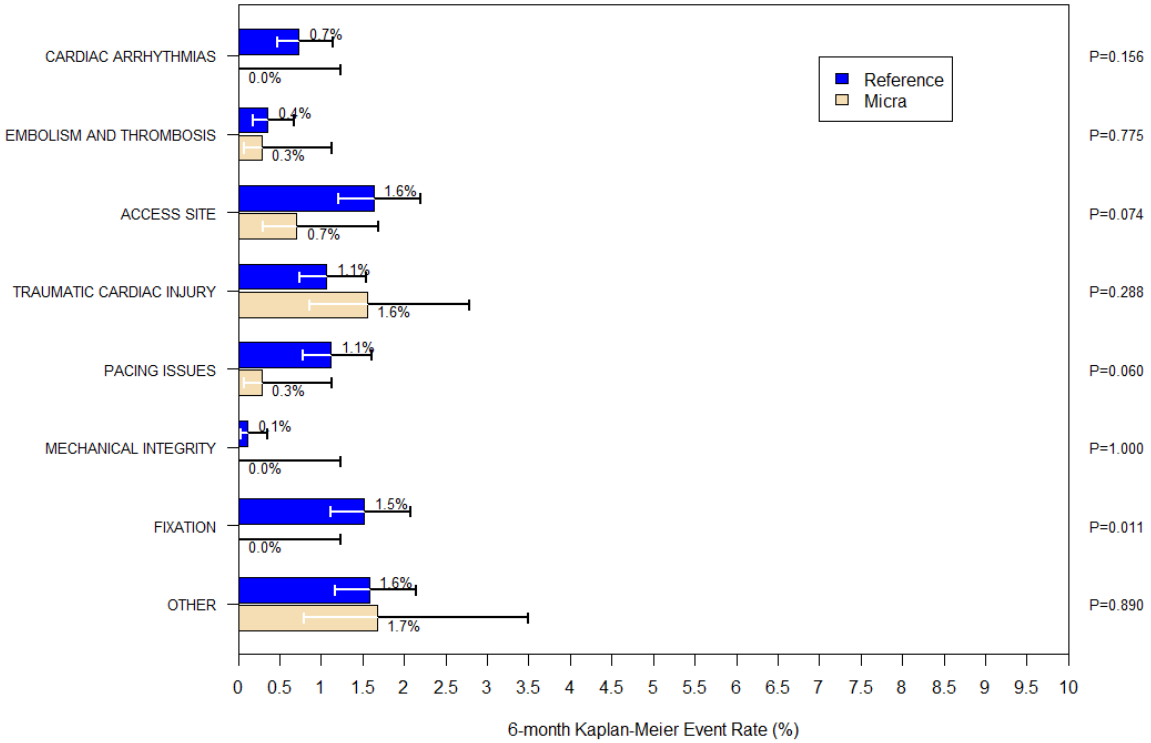
Note: n is the number of subject remaining at risk 183 days post-implant.

The total population from the six (6) previous studies included 2667 subjects. Post-hoc analysis comparing the freedom from major complication rates at 6-months post-implant between the 725 subjects with a Micra implant attempt and all 2667 subjects demonstrates that the 6-month major complication rate was lower for Micra than the leaded pacemaker systems (4.0% Micra vs 7.4% leaded systems, post-hoc P=0.006). A two-sided statistical test of the 6-month freedom rates based on the Kaplan-Meier estimates was constructed using log-log transformation of each Kaplan-Meier estimate. If no events were observed in one of the datasets, Fisher's Exact test was used to compare the groups.

Figure 4 displays the 6-month major complication rates as estimated using the Kaplan-Meier method for Micra and the reference pacemaker study subjects by major complication category. The lower rate of major complications observed

with the Micra system relative to the six (6) reference Medtronic pacemaker studies appeared to have been largely driven by reductions in access site events (primarily implant site haematoma and implant site infections), pacing issues (primarily device capture and device pacing issues), and fixation events (there were no device/lead dislodgements in the Micra study). Of note the rate of major complications related to cardiac injury (i.e., pericardial effusion or perforation) were higher in the Micra study than in the six reference Medtronic pacemaker studies (P=0.288).

Figure 4: 6-Month Major Complication Rates by Category (Micra vs Reference Dataset – All 2667 Reference Subjects)



Notes: Confidence intervals are based on log-log transformation of the survival estimate except in cases where zero events were observed (mechanical integrity and fixation) where they are based on the exact binomial distribution.
P-value based on comparison of Kaplan-Meier estimates at 183 days post-implant except in cases where zero events were observed in one group. In this case the P-value is based on Fisher's exact test.

Conclusion

There were 28 major complications in 25 subjects related to the Micra system or procedure as determined by the CEC occurring in the 725 subjects with a Micra implant attempt during a total of 3124.1 months of follow-up. The Kaplan-Meier estimate for the freedom from major complications related to Micra system or procedure at 6-months (183 days) post-implant was 96.0% (98.66% CI: 93.3% - 97.6%). This was higher than the pre-specified performance criterion of 83% (P<0.0001). Since the p-value associated with this test was lower than the p-value

required to reject the null hypothesis at the first interim analysis (0.0067), the null hypothesis was rejected and the primary safety objective was considered met.

2. Effectiveness Results

The analysis of effectiveness was based on the 300 evaluable patients at the 6-month time point. Key effectiveness outcomes are presented below. Clinical review indicates that the device functioned as expected in the indicated patient population.

Primary Effectiveness Objective

At the time of the visit cutoff, there were 301 6-month visits among the 719 successfully implanted subjects. Of the 301 subjects with 6-month visits, 295 (98.7%) had their PCT measured at 0.24 ms using the pre-specified auto decrement test at both the implant and 6-month visit and were included in the main analysis of this objective. Figure 5 outlines the data available for the effectiveness objective and Table 12 outlines the data for adequate 6-month PCT.

Figure 5: Data Available for Primary Efficacy Objective

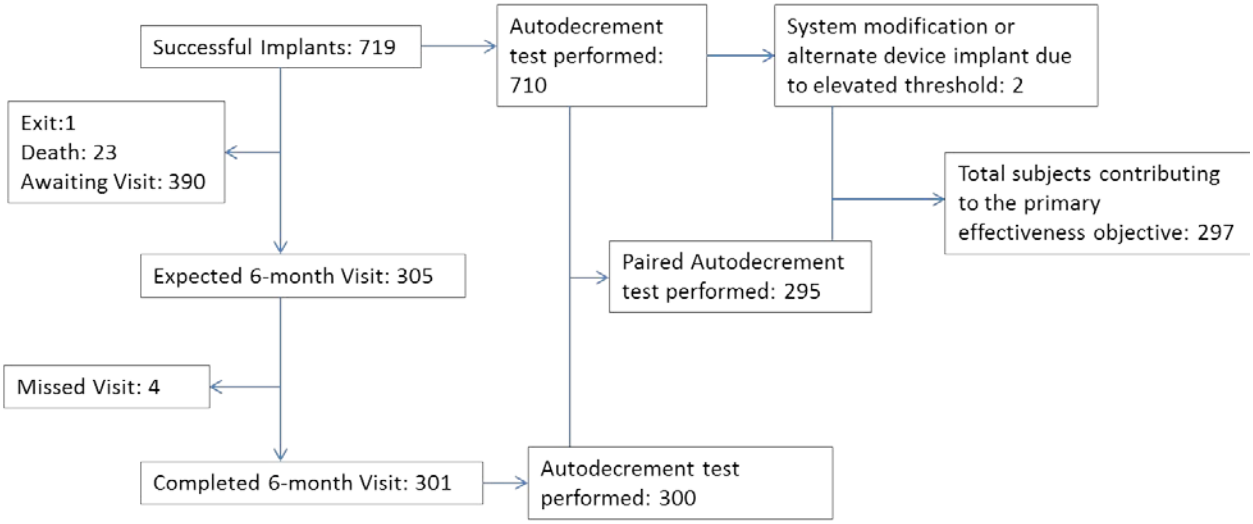


Table 12: Percent Subjects with Adequate 6-month PCT

Subjects[1]	Subjects with Adequate 6-Month PCT	% Subjects with Adequate 6-Month PCT	98.66% CI[2]	Performance Goal	Nominal One-sided P-value[3]
297	292	98.3%	(95.4%, 99.6%)	80%	<0.0001

[1]Subjects with paired implant and 6-month auto decrement PCT values (0.24 ms), or who had a system modification or alternative device implant prior to 6 months due to elevated threshold.
[2]Confidence interval coverage probability dictated by the Hwang-Shih-DeCani alpha spending function.
[3]P-value from Exact Binomial test.

There were 10 subjects who could have completed the primary efficacy endpoint but did not due to missing data or missed visit, and 24 subjects who exited or died prior to completing their 6-month visit. These 34 additional subjects were further evaluated below to assess the robustness of the primary efficacy objective results. Following the pre-specified missing data imputation rules (values for 7 subjects imputed) and assuming that subjects whose data could not be imputed were failures (remaining 27 subjects) the percentage of subjects meeting the primary efficacy endpoint was 90.3% with a 98.66% CI of 85.6% - 93.9%.

Conclusion
Of the 297 subjects who contributed to the primary efficacy analysis, 292 (98.3%) had an adequate 6-month PCT, meaning they had a 6-month PCT no greater than 2.0V and had a rise in PCT from implant to 6-months of no more than 1.5V.

This observed percentage of subjects with an adequate safety margin was greater than the pre-specified goal of 80% since the nominal one-sided P-value was lower than the nominal alpha level of 0.0067 dictated by the Hwang-Shih-DeCani alpha spending rule. Therefore the null hypothesis associated with the primary efficacy objective was rejected and the primary efficacy objective was considered met.

3. Secondary Objectives Results

Secondary Objective #1
Of the 301 subjects with 6-month visits, 280 (93.0%) had their PCT measured using both the manual (auto decrement) test and the VCM test measured at 0.24 ms, and were included in the main analysis of this objective. There were 25 subjects who were successfully implanted with the Micra system, but were not included in the main analysis of this objective due to missing data (missed 6-month visit – 4, capture management threshold test did not complete successfully due to high heart rate – 20, auto decrement test was not performed – 1). None of the subjects failed to capture using either the auto decrement or VCM test at these 6-month visits. Figure 6 outlines the data available for the first secondary

objective and Table 13 outlines the accurate 6-month ventricular capture management values.

Figure 6: Data Available for Secondary Objective #1

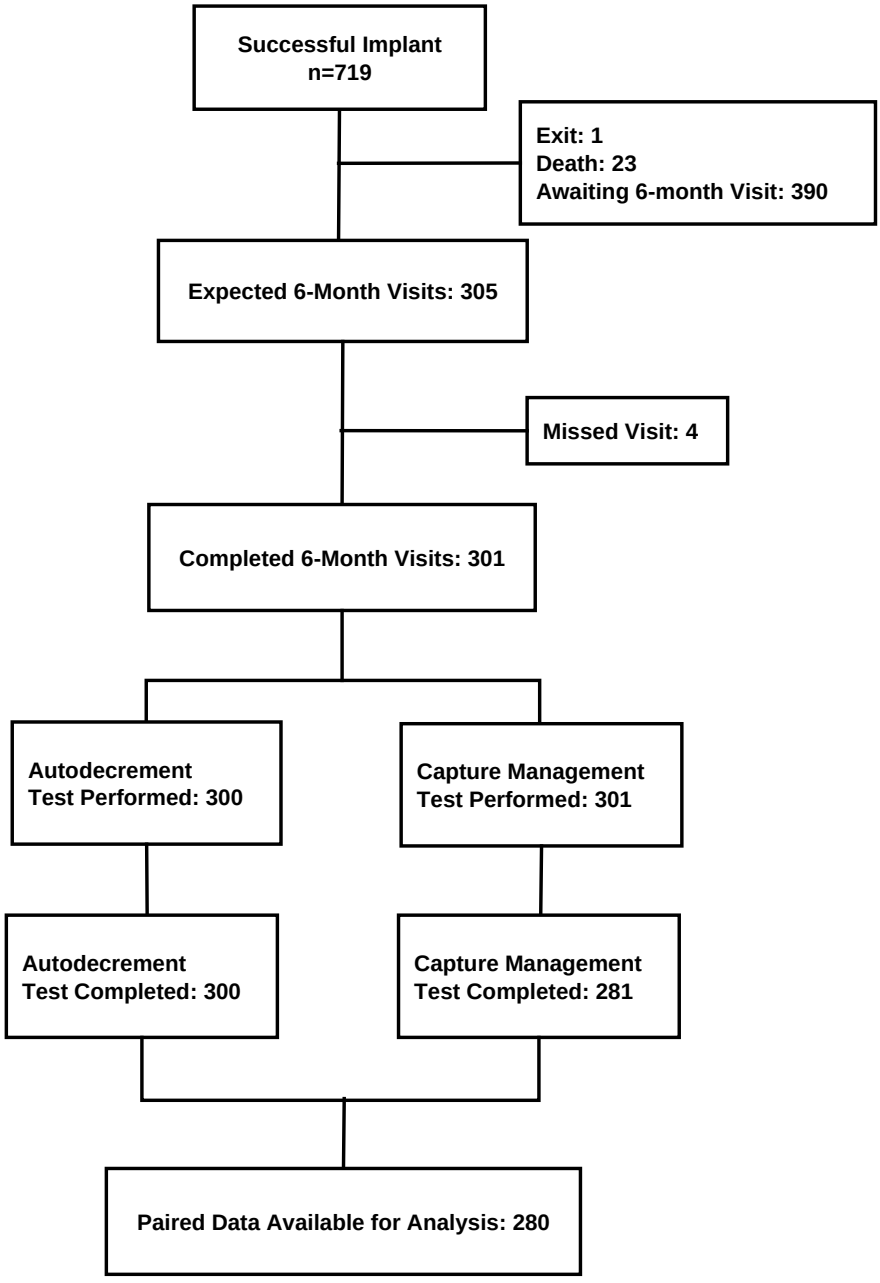


Table 13: Percent of Subjects with Accurate 6-month Ventricular Capture Management Values

Subjects[1]	Subjects with Accurate VCM Value[2]	% Subjects with Accurate VCM Value	98.66% CI[3]	Performance Goal	Nominal One-sided P-value[4]
280	279	99.6%	(97.5%, 100.0%)	85%	<0.0001

[1]Number of subjects with paired VCM and auto decrement PCT data available at the 6-month visit.
[2]Number of subjects with a VCM PCT within ±0.5V (inclusive) of the auto decrement PCT measured at 0.24ms.
[3]Confidence interval coverage probability dictated by the Hwang-Shih-DeCani alpha spending function.
[4]P-value from Exact Binomial test.

Of the 280 subjects with paired 6-month auto decrement and VCM PCT values, 279 (99.6%) had VCM values within ± 0.5V of the auto decrement PCT value. There was no systematic deviation between the PCT measurements across the range of PCT values.

This percentage was greater than the pre-specified goal of 85% since the Holm adjusted P-value (i.e. twice the nominal one-sided P-value) was lower than the nominal alpha level of 0.0067 dictated by the Hwang-Shih-DeCani alpha spending rule. Therefore, secondary objective #1 was considered met.

Secondary Objective #2

M-PREP exercise tests were attempted by 40 subjects at the 3-month visit and 29 subjects at the 6-month visit with 27 subjects attempting M-PREP tests at both the 3-month and 6-mont visit. For an M-PREP test to be included in the analysis of this objective, subjects needed to reach at least stage 4 of the M-PREP test protocol without continually using the treadmill handle bars to ensure that the rate response feature could be adequately tested. Table 14 provides the accountability of all 69 M-PREP test attempts and indicates that the most common reason for not using an M-PREP test in the analysis was for not reaching stage 4 of the test protocol. There were 30 usable M-PREP tests (15 at the 3-month visit and 15 at the 6-month visit) from 20 unique subjects that were included in the analysis of the objective.

Table 14: Summary of Attempted M-PREP Tests

M-MPREP Test Status	**3-Month Test (N = [illegible])**	**6-Month Test (N = [illegible])**	**Total (N = 69)**
Continuous handle bar use	7 (17.5%)	9 (31.0%)	16 (23.2%)
Stage 4 not reached	18 (45.0%)	5 (17.2%)	23 (33.3%)
Incorrectly performed M-PREP	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing device interrogation file	0 (0.0%)	0 (0.0%)	0 (0.0%)
Usable M-PREP test	**15 (37.5%)**	**15 (51.7%)**	**30 (43.5%)**

Notes: Of the 27 subjects that attempted M-PREP tests at both the 3-month and 6-month visit 10 had usable M-PREP tests at both visits.

Figure 7 displays the normalized rate response for each of the 30 usable M-PREP treadmill tests by plotting the normalized sensor rate (scaled so the sensor rate is 0 at rest and 1 at the maximum M-PREP state reached) versus normalized workload (scaled so that a value of 0 is rest and a value of 1 is maximum workload). These data show that in general the sensor rate increased proportionally to workload for all treadmill tests.

Figure 7: Normalized Sensor Rate versus Normalized Workload for 30 Useable M-PREP Treadmill Tests

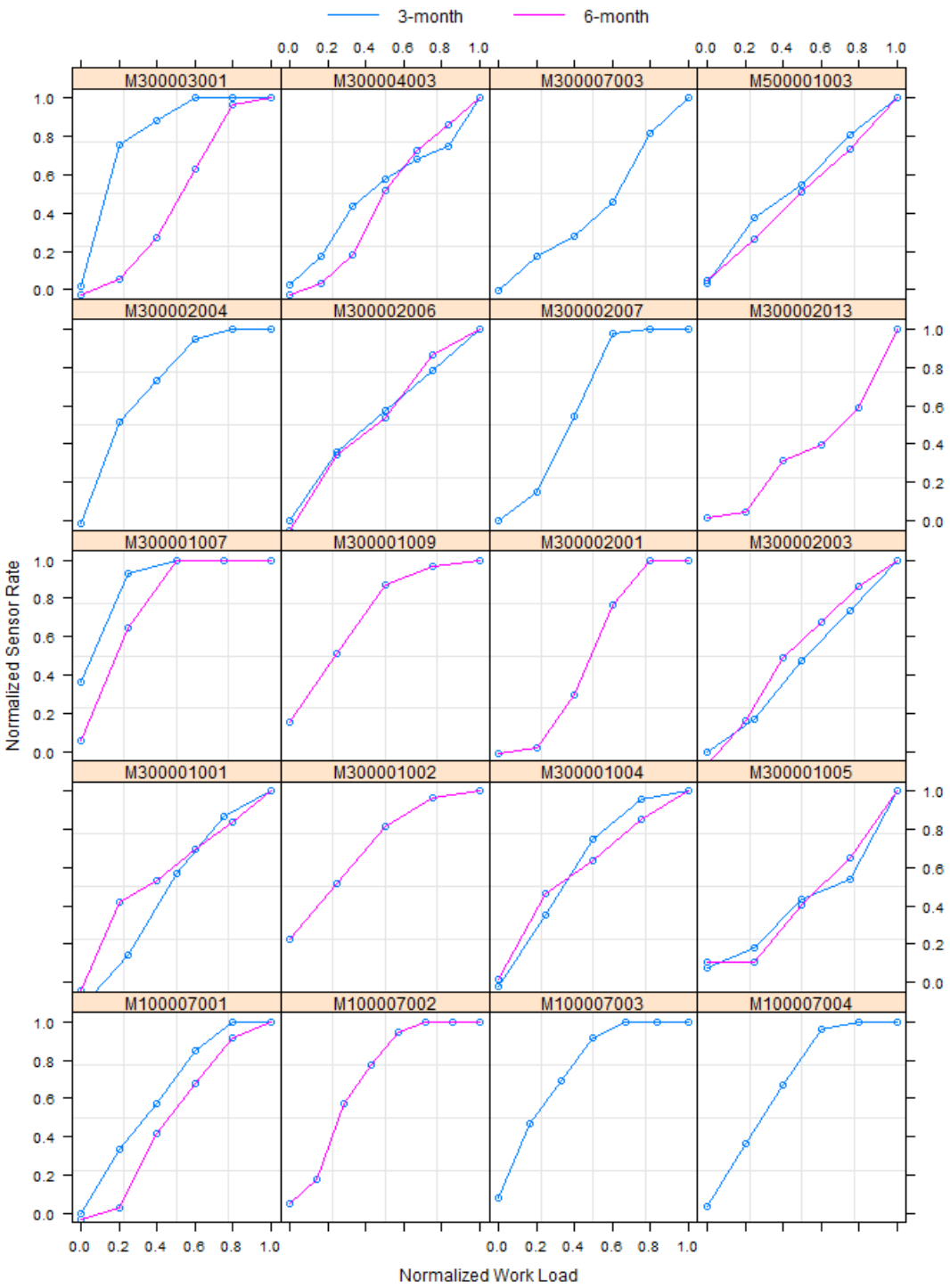


Table 15 shows that the slope parameter for the Kay-Wilkoff model for the combined 3-month and 6-month visits was 0.864 with a nominal two sided 90% CI ranging from 0.768 to 0.961. Since this confidence interval lies completely within the equivalence margin of 0.65 to 1.35 the null hypothesis was rejected and

it was concluded that the Micra system provided adequate rate response (TOST P-value: <0.001).

Table 15: Metabolic-Chronotropic Response based on Kay-Wilkoff Slope Parameter

Visit	Attempted Treadmill Tests	Usable M-PREP Tests	Kay-Wilkoff Slope Parameter	90% Confidence Interval	Nominal TOST[1] P-value
Combined[2]	63	30	0.864	0.768-0.961	<.001
3-month	37	15	0.839	0.716-0.962	<.008
6-month	26	15	0.850	0.731-0.969	<.005

[1]TOST = Two one-sided test procedure.
[2]P=0.799 for test of visit by normalized work load interaction.

The rate response operation of the Micra system was confirmed by demonstrating that the slope parameter from the Kay-Wilkoff model fell within an equivalence margin of 0.65 to 1.35. Since Holm adjusted P-value for Secondary Objective #1 was less than the critical value, Secondary Objective #2 (rate response) could be tested at the nominal 0.05 level using the TOST procedure. Additional patients will be evaluated post approval to reach 95% confidence in the rate response feature.

E. Financial Disclosure:

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 205 investigators of which none were full-time or part-time employees of the sponsor and 8 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 8
- Significant payment of other sorts: 0
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The following subgroups were prospectively defined: sex, geography, and pacing dependence (yes/no). Table 16 displays the freedom from major complications related to the Micra system or procedure at 6-months by pre-specified subgroups as well as by specific geographical entities.

Table 16: 6-Month Major Complication Freedom Rates by Subgroup

Parameter	Subgroup	Subjects with Implant Attempt (%)	Kaplan-Meier Freedom Rate at 6 Months (95% CI)	P-value[1]
Geography - US vs OUS*	US	284 (39.2%)	94.5% (90.6%, 96.8%)	0.0668
	OUS	441 (60.8%)	96.9% (94.3%, 98.3%)	
Sex	Male	426 (58.8%)	97.5% (95.0%, 98.7%)	0.0185
	Female	299 (41.2%)	93.8% (89.8%, 96.2%)	
Pacemaker Dependent[2]	No	705 (97.2%)	95.8% (93.8%, 97.2%)	0.3996
	Yes	20 (2.8%)	100.0% (NA)	

*These subgroups were not pre-specified in the Micra CIP or statistical analysis plan, but were added at the request of worldwide regulatory authorities.

[1]P-value from log-rank test testing for heterogeneity (i.e., non-poolability) in major complication rates by subgroup.

[2]Pacemaker dependence defined as an escape rhythm ≤ 30 bpm.

A. US versus OUS

A set of exploratory analyses were performed in order to understand the source of the heterogeneity observed in the primary safety objective results among those subjects with an implant attempt in the US versus those with an implant attempt outside of the US (OUS). The 284 subjects in the US with a Micra implant attempt generally had a higher rate of major complications across all event groupings compared to the 441 subjects OUS with a Micra implant attempt. The one exception was "events at the groin puncture site" where OUS subjects tended to have a higher rate than US subjects.

Of note, the 284 subjects with a Micra implant attempt in the US were more likely to have a primary pacing indication associated with sinus node dysfunction and less likely to have pacing indications associated with AV block or other indications compared to their 441 OUS counter parts. Additionally, subjects in the US were more likely to have pacing indications associated with persistent/permanent atrial tachyarrhythmias than OUS subjects. In the US, the reason for selecting a single chamber pacemaker was more likely associated with significant co-morbidities affecting survival or clinical outcome, indications associated with

persistent/permanent/chronic atrial tachyarrhythmias, previous or planned AV node ablation, subject's sedentary lifestyle, and value of new technology.

Conversely, the reason for selecting a single chamber pacemaker OUS was more likely to be because frequent pacing was not expected. Finally, the subjects in the US had more co-morbidities and were more likely to have a medical history including congestive heart failure, coronary artery disease, hypertension, pulmonary hypertension, tricuspid valve dysfunction, COPD, diabetes, renal dysfunction, and chronic lung disease.

Results of the competing risk models exploring the heterogeneity between the major complication freedom rate in US and OUS subjects suggest that the risk for Micra related major complications are more related to a subject's underlying medical condition than the geography where the Micra implant procedure occurred. Thus, after adjusting for underlying subject medical condition, the primary safety objective results are poolable between the US and OUS geographies.

B. Major Complication Rates by Sex

Another set of exploratory analyses were performed in order to understand the source of the heterogeneity observed in the primary safety objective results among males and females.

Table 17: Freedom from Major Complications Related to the Micra System or Procedure by Sex at 6-Months Post-implant

Sex	6-month Major Complication Freedom Rate (98.66% CI)	Performance Goal	P-value[1]
Male	97.5% (94.1%, 99.0%)	83%	<0.0001
Female	93.8% (88.4%, 96.7%)	83%	<0.0001

[1]P-value comparing Kaplan-Meier estimate of 6-month major complication freedom rate to 83%.

Table 17 suggests that the higher major complication rate observed in females was largely due to the higher rate of cardiac injury observed in females relative to males. Several large cohort studies of leaded cardiac devices have also shown a higher rate of complications in females (see for example Hsu, et al 2013[5], Udo, et al 2012[6],

[5] Hsu, JC, Varsoy, PD, Bao, H, et. al. 2013. Cardiac Perforation from Implantable Cardioverter-Defibrillator Lead Placement: Insights from the National Cardiovascular Data Registry. Circ Cardiovasc Qual Outcomes 6:582 – 590.

[6] Udo, EO, Zuithoff, NP, van Hemel NM, et. al. 2012. Incidence and predictors of short- and long-term complications in pacemaker therapy: The FOLLOWPACE study. *Heart Rhythm* 9:728-735.

Haines, et al. 2011[7], Lee et al 2010[8]). Thus, it is plausible that females have an inherent higher risk for complications associated with the Micra implant compared to males similar to other cardiac devices.

Table 18: System or Procedure Related Major Complications by Sex

	No. Events (No. Subjects, %)	
Adverse Event Key term	**Male Subjects (n=426)**	**Female Subjects (n=299)**
Total Major Complications	**11 (9, 2.11%)**	**17 (16, 5.35%)**
Embolism and Thrombosis	**1 (1, 0.23%)**	**1 (1, 0.33%)**
Deep Vein Thrombosis	1 (1, 0.23%)	0 (0, 0%)
Pulmonary Embolism	0 (0, 0%)	1 (1, 0.33%)
Events at Groin Puncture Site	**3 (3, 0.70%)**	**2 (2, 0.67%)**
Arteriovenous Fistula	3 (3, 0.70%)	1 (1, 0.33%)
Vascular Pseudoaneurysm	0 (0, 0%)	1 (1, 0.33%)
Traumatic Cardiac Injury	**3 (3, 0.70%)**	**8 (8, 2.68%)**
Cardiac Perforation	0 (0, 0%)	3 (3, 1.00%)
Pericardial Effusion	3 (3, 0.70%)	5 (5, 1.67%)
Pacing Issues	**1 (1, 0.23%)**	**1 (1, 0.33%)**
Device Dislocation	1 (1, 0.23%)	0 (0, 0%)
Device Pacing Issue	0 (0, 0%)	1 (1, 0.33%)
Other	**3 (3, 0.70%)**	**5 (5, 1.67%)**
Acute Myocardial Infarction	0 (0, 0%)	1 (1, 0.33%)
Cardiac Failure	1 (1, 0.23%)	2 (2, 0.67%)
Metabolic Acidosis	0 (0, 0%)	1 (1, 0.33%)
Pacemaker Syndrome	1 (1, 0.23%)	0 (0, 0%)
Presyncope	0 (0, 0%)	1 (1, 0.33%)
Syncope	1 (1, 0.23%)	0 (0, 0%)

Female subjects were more likely to be shorter, weigh less, have a reason for single chamber pacemaker selection of "prior or planned AV nodal ablation," and have a history of congestive heart failure compared to their male counterparts. Males were more likely than females to have a history of coronary artery disease and myocardial infarction.

For all models the competing risk was death unrelated to the Micra system or procedure. The results of the competing risk models suggest that much of the heterogeneity in risk for Micra related major complications between males and

[7] Haines, DE, Wang, Y, Curtis, J. 2011. Implantable Cardioverter-Defibrillator Registry Risk Score Models for Acute Procedural Complications or Death After Implantable Cardioverter-Defibrillator Implantation. Circulation 123: 2069-2076.

[8] Lee, DS, Krahn, AD, Healey JS, et al 2010. Evaluation of early complications related to *de novo* cardioverter defibrillator implantation. JACC 55:774-782.

females may be explained by body habitus (specifically weight) and the need for AV nodal ablation. However, given that females tend to have a smaller body habitus relative to males it is plausible that female sex is an important risk factor for complications associated with cardiac rhythm device implant procedures in general.

Traumatic cardiac injuries resulted in tamponade and open surgical repair. The clinical outcomes suggest that cardiac injury events occur at higher rates and are more severe than conventional pacemaker systems. Vascular injuries due to the implantation site have resulted in additional hospitalization due to excessive bleeding and AV fistulas. These events are not observed in conventional systems. However, benefits would outweigh these risks for patients who have poor venous access.

C. Implant Procedure Evaluation

The firm also collected information on the implant procedure and device handling by implanting physicians and subjects in multiple geographies. The following were characterized about the implant procedure by electronic case report forms: success rate, fluoroscopy time, changes to anticoagulation medications, tine engagement, and hospital stay. The implant procedure has been successfully performed by 94 physicians in 56 study centers with the majority of physicians describing the procedure as "easy" or "extremely easy." In the few cases where a clinician shared dissatisfaction, the following lessons were learned and incorporated into device labeling: unusual patient anatomy may make navigation to the RV difficult; clot can form on the device during implant; and how to visualize tine movement.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel for single chamber, transvenous pacemaker systems.

However, a general issues panel meeting for the class of leadless pacemakers was held on February 18, 2016. The panel was asked to discuss and provide recommendations on the acute adverse event rates noted in available clinical trial information, post approval study design considerations, device labeling, and indications for use for leadless pacemakers. The panel recommended the following:

- Expectations of cardiac perforation rates should be consistent with rates of transvenous systems.
- No subgroups need to be excluded from receiving a leadless pacemaker.
- Implanting physicians should be adequately trained/informed about adverse events and patient selection.
- Acute and long term events should be captured via a post approval study.
- Post approval study sample size is acceptable to be 1741 patients, with at least 500 followed for 9 years.

- Data from a total of 200 end-of-life cases, including device removal/extraction experience, where applicable, should be collected.
- Labeling should be device-specific and incorporate device experience, noting limitations of knowledge gaps, where appropriate.
- Indications for use of transvenous, single chamber pacemakers apply to this class of devices and AHA/ACC/HRS guidelines are already applicable.

These recommendations were considered in the course of this review as they applied to leadless pacemakers in general. The panel meeting transcript can be found at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM489547.pdf

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The percentage of subjects with a low (≤2V) and stable (≤1.5V rise from implant) pacing capture threshold measured at 0.24ms at 6-months post-implant was 98.3% (CI: 95.4% - 99.6%) exceeding the pre-specified performance goal for the primary effectiveness objective of 80% (P<0.0001). The low and stable thresholds observed with Micra result in an estimated average battery longevity of 12.5 years based on actual device use conditions through 6-months of follow-up.

The accuracy of Micra's ventricular capture management feature was confirmed as 99.6% of subjects (98.66% CI: 97.5% - 100%) had a ventricular capture management threshold within 0.5V of the manually performed auto decrement threshold at 6-months post implant exceeding the pre-specified performance goal of 85%. Rate responsiveness of the Micra system was also confirmed based on 30 treadmill tests. Additional treadmill tests post approval with new individual patients will be performed to further characterize the performance of the rate response feature.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The freedom from major complications at 6-months post-implant among the 725 subjects with a Micra implant attempt was 96% (98.66% CI: 93.3% - 97.6%), exceeding the pre-specified performance criterion of 83% derived from 977 subjects with atrial fibrillation (AF) from 6 previous pacemaker studies (P<0.0001).

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. When Micra was compared to the reference pacemaker datasets in Table 1, Micra demonstrated a significant

reduction in total major complications at 6 months (4.0% for Micra vs 7.4% for traditional technology, P=0.006). Micra appeared to reduce the rate of major complications associated with cardiac arrhythmias, the access site, and device fixation compared to the reference datasets used to derive the performance criterion. Additionally, there have been no reports of gross device dislodgement during the follow-up period and no observations of device orientation change based on X-ray analysis at the 3-month and 12-month visits suggesting robust device fixation. Additionally, as noted above, traumatic cardiac injuries resulted in tamponade and open surgical repair. The clinical outcomes suggest that cardiac injury events occur at higher rates and are more severe than conventional pacemaker systems. Vascular injuries due to the implantation site have resulted in additional hospitalization due to excessive bleeding and AV fistulas. These events are not observed in conventional systems. However, benefits for patients who cannot undergo a transvenous implant due to poor venous access would outweigh these risks.

Limitations include the lack of option for dual chamber upgrade or VDD lead, currently available for transvenous systems.

Additionally, further data collection is necessary to determine the practicality of long term device extraction or technique. The clinical study was not of sufficient duration to allow evaluation of the extraction of the device in regards to practicality, safety of techniques, or to recommend what to do with expired devices at the time of replacement. Currently, it is recommended for the device to be turned off and remain in place. Considering no infections were observed, this seems to be acceptable until additional data becomes available and device labeling can be updated.

An additional factor to be considered in determining probable risks and benefits for the Micra TPS device is novelty of the device design, removing the need for transvenous access, and a cardiac lead in the system. This removes the risk of pocket infection and common lead-related issues, such as fractures. However, cardiac injury increased the risk of major complications.

In conclusion, given the available information above, the data support that for the above stated indications for use of the device the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications of use. The Micra TPS demonstrated safety and effectiveness by passing its pre-specified primary safety and effectiveness objectives after 725 subjects underwent implant attempt (719 successful, 99.2%) and 301 subjects completed the 6-month post-implant visit.

In summary, the safety experience showed:

- Low 6 month major complication rate compared to Medtronic reference dataset (4% Micra versus 7.4% in 2667 patients from 6 previous Medtronic studies)
- Low rate of system revision (explant, reposition, replacement) (3 in 725 = 0.4%). The occurrences included 1 Micra retrieval with a new Micra implanted and 2 patients where the Micra remained in the body and a traditional pacing system was implanted.
- No unforeseen events (0%)
- No device telemetry issues (0%)
- No gross dislodgements (0%)
- No systemic infections (0%)

The implant procedure and device handling have been evaluated by implanting physicians and subjects in multiple geographies. The implant procedure has been successfully performed by 94 physicians in 56 study centers with the majority of physicians describing the procedure as "easy" or "extremely easy." The observed learning curve indicates the need for appropriate training at clinical sites.

Long term monitoring of all successfully implant subjects continues and the study's pre-specified long-term safety objective will be evaluated once all successfully implanted subjects have the opportunity to complete their 12-month post-implant visit. A post approval study will evaluate acute and long term device experience and collect as much information as possible on end-of-life options for the device to further characterize the system and update recommendations accordingly.

The device and implant procedure has met or exceeded all of its planned objectives. Thus, the data provide reasonable assurance of the safety and effectiveness of the Micra system when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on April 6, 2016. The final conditions of approval cited in the approval order are described below.

ODE Lead PMA Post-Approval Study - Micra Rate Response Confirmation Study: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The Micra Rate Response Confirmation Study is a confirmation study for the rate response feature of the device. It aims to collect additional treadmill testing data from subjects for at least 3 months. The study is a non-significant risk, prospective, non-randomized multi-center clinical research study. The study is expected to be conducted in up to 4 centers in up to 50 subjects over 12 months. The primary objective is to confirm the rate response operation of the Micra system in at least 15 additional patients to supplement the data collected during the pre-market investigational device exemption study. The protocol was received via email on March 8, 2016. The PAS progress reports should be submitted every six months until study completion.

OSB Lead PMA Post-Approval Study - Micra™ Transcatheter Pacing System Post-Approval Study: The Office of Surveillance and Biometrics (OSB) will have the lead for study initiated after device approval. This study will be conducted as per protocol dated March 8, 2016, Version 2. Micra System Post-Approval Study (PAS) is to evaluate safety and effectiveness of the system when used as intended. Micra PAS is a global, prospective, observational, multi-center study. The primary objectives of this PAS are to estimate acute (≤ 30 days) complication rate related to the Micra system and/or implant procedure and the 9-year complication free survival rate of the Micra system. The secondary objective is to characterize treatment and/or procedure related to Micra system end of device service. There will be 1830 patients enrolled to ensure 1741 patients undergoing Micra system implant procedure for the acute complication rate estimation, 500 patients for the 9-year complication free survival rate estimation, and a minimum of 200 patients with a Micra system revision for characterizing Micro end of device service. The PAS progress reports should be submitted every six months during the first two years an annually thereafter.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

[1]Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. ACC/AHA/HRS 2008 Guidelines for Device-based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). 2008.

[2]Europace 2006 8. 746-837 doi:10.1093/europace/eul108

[3]Udo et al for the FOLLOWPACE Study. Heart Rhythm 2012;9:728 –735

[4]Kay, GN. 1992. Quantitation of chronotropic response: comparison of methods for rate-modulating permanent pacemakers. JACC 20 (7) 1533 – 1541.

[5]Hsu, JC, Varsoy, PD, Bao, H, et. al. 2013. Cardiac Perforation from Implantable Cardioverter-Defibrillator Lead Placement: Insights from the National Cardiovascular Data Registry. Circ Cardiovasc Qual Outcomes 6:582 – 590.

[6]Udo, EO, Zuithoff, NP, van Hemel NM, et. al. 2012. Incidence and predictors of short- and long-term complications in pacemaker therapy: The FOLLOWPACE study. Heart Rhythm 9:728-735.

[7]Haines, DE, Wang, Y, Curtis, J. 2011. Implantable Cardioverter-Defibrillator Registry Risk Score Models for Acute Procedural Complications or Death After Implantable Cardioverter-Defibrillator Implantation. Circulation 123: 2069-2076.

[8]Lee, DS, Krahn, AD, Healey JS, et al 2010. Evaluation of early complications related to de novo cardioverter defibrillator implantation. JACC 55:774-782.