Biotronik, Inc.

Entovis ProMRI Pacemaker System Labeling and Programmer Software Version PSW 1307.U

PURPOSE OF SUBMISSION

The firm is requesting approval for MRI-conditional labeling for the Entovis SR / SR T / DR / DR-T pacemakers and the supporting Programmer Software Version PSW 1307.U. When an Entovis Pacemaker is used in conjunction with Setrox S 53/60 or Safio 53/60 pacemaker leads, the system will be identified as the Entovis ProMRI Pacemaker System. More specifically, the firm is requesting approval for the Entovis ProMRI Pacemaker System technical manual, which includes all of the MRI-relevant information for the system. In addition, the firm has requested approval for minor modifications to the Entovis Pacemaker (pulse generator) technical manual including a reference the Entovis ProMRI Pacemaker System technical manual and removal of the blanket Warning and Precaution related to MRI.

The Entovis pacemakers were previously approved by FDA under P950037/S072. The Setrox pacemaker leads were previously approved by FDA under P950037/S042. Safio is an alternate trade name for the Setrox pacemaker leads. The Programmer Software Version PSW 1307.U is based on the PSW 1301.U, which was approved by FDA under P050023/S069. The only change to the software is related to the introduction of an MRI mode.

The firm conducted verification/validation testing, modeling, supporting bench testing, animal testing, and clinical studies using the FDA approved Entovis pacemaker as well as the Setrox/Safio pacemaker leads in order to demonstrate the safety and performance of these components when used as a system under specific MRI conditions.

Background Information

There were numerous previous interactions with the firm leading to this submission including the following files: (b)(4) TS/CCI), G120226 (b)(4) TS/CCI (b)(4) TS/CCI), Q130583, and Q131607. As a result, most of FDA's questions and concerns had been shared and discussed with the firm, even before submission of this PMA Supplement, in the letters for IDE submissions or during interactive face-to-face meetings.

Most importantly, FDA met face-to-face with the firm as part of Q131607. The purpose of the meeting was to discuss and address multiple "future concerns" that FDA had included in the IDE approval letters for G120226, which includes the devices being reviewed in this PMA Supplement. The meeting for Q131607 occurred on February 4, 2014, shortly before FDA completed its review of the PMA Supplement and FDA's decision to "proceed interactively." The timing of the meeting corresponded with the time that the FDA review team was completing its review of the PMA Supplement, which allowed us to discuss the non-clinical questions directly with the sponsor. Therefore, the primary focus of the review following this meeting was on the clinical study results, statistical analyses, and labeling.

DEVICE DESCRIPTION

The devices included in the submission are pacemakers (product code LWP) and pacemaker leads (product code NVN). More specific descriptions of the devices are included in the Indication for Use statements in the following section.

The following text was provided by the sponsor to explain the various trade names and models that are referenced in the submission.

> *On October 3, 2012, BIOTRONIK submitted an Original IDE for the ProMRI study to evaluate the safety and effectiveness of the Entovis ProMRI system (same hardware as Evia pulse generator) when used under specific MRI conditions (G120226). FDA sent an IDE approval with conditions letter on December 21, 2012.*
>
> *BIOTRONIK decided to restrict the ProMRI study to the legally marketed Entovis pulse generator product name instead of the Evia pulse generator to better control subject access enrolled in the ProMRI study and who had access to the MRI mode available with the* (b)(4) TS/CCI (b)(4) TS/CCI *The Entovis pulse generators were approved through P950037/S072, dated May 7, 2010 as part of the Evia family of pulse generators due to the fact that both devices have the identical hardware. The only difference between the Evia and Entovis devices is that Entovis does not have the software-based EasyAV feature, which is an additional diagnostic feature that has no clinical impact on the patient. There are no other differences between these devices. BIOTRONIK is proposing Safio as an alternate trade name for BIOTRONIK's legally marketed Setrox leads (P950037/S042, dated February 14, 2006). BIOTRONIK has taken the data from the ProMRI study and has pooled it with data from the ProMRI AFFIRM study which was conducted outside the US. The ProMRI AFFIRM study included Evia and Safio devices.*
>
> *With this PMA Supplement, BIOTRONIK is requesting approval for use of the Entovis ProMRI System which includes the Entovis pulse generators and Setrox / Safio leads in the described MR environment.*

The submission included various other names for the pacemakers and pacemaker leads. However, the sponsor clarified that

- All references to Evia within the testing documents and prior FDA submissions are synonymous with the Entovis pulse generators.
- All references to Safio within the testing are synonymous with the Setrox S leads.

INDICATIONS FOR USE

There were no changes to the indications for use, which are provided below.

Entovis Pulse Generators

Rate-adaptive pacing with the Entovis pulse generators is indicated for patients exhibiting chronotropic incompetence and who would benefit from increased pacing rates concurrent with physical activity.

Generally accepted indications for long-term cardiac pacing include, but are not limited to: sick sinus syndrome (i.e. bradycardia-tachycardia syndrome, sinus arrest, sinus bradycardia), sino-atrial (SA) block, second- and third- degree AV block, and carotid sinus syndrome.

Patients who demonstrate hemodynamic benefit through maintenance of AV synchrony should be considered for one of the dual chamber or atrial pacing modes. Dual chamber modes are specifically indicated for treatment of conduction disorders that require both restoration of rate and AV synchrony such as AV nodal disease, diminished cardiac output or congestive heart failure associated with conduction disturbances, and tachyarrhythmias that are suppressed by chronic pacing.

Setrox / Safio S Pacing Leads

BIOTRONIK's Setrox/Safio S transvenous, steroid-eluting, active fixation endocardial leads are indicated for permanent pacing and sensing. Active fixation pacing leads with a bipolar (BP) IS-1 connector configuration are designed for use in conjunction with implantable pulse generators with IS-1 headers. The leads may be used with single or dual chamber pacing systems.

The Setrox/Safio S lead models are intended for placement in either the right atrium or right ventricle.

PROPOSED MR LABELING

The firm is requesting approval to use the following MR labeling:

MRI Conditions for Use

The Entovis ProMRI Pacemaker System Technical Manual (Appendix 99), which is a special manual, separate from the Entovis pulse generator manual, includes the following requirements that must always be fulfilled in order to perform an MR scan using BIOTRONIK's Entovis ProMRI Pacemaker System:

- The device system consists of a pacemaker with one or two pacing leads in combination to constitute an MR conditional device system (See p. 5 of the Entovis ProMRI manual).
- There must be no other implanted medical devices that may interact with MRI, such as
    - abandoned pacemaker/ICD leads
    - lead extensions
    - other active medical devices
    - non-MRI compatible devices
- The absence of phrenic nerve stimulation at 4.8 V at 1.0 ms.
- The leads have been implanted for at least 6 weeks.
- The device system is implanted pectorally.
- The measured pacing threshold is not above 2.0 V at 0.4 ms pulse width.
- The pacing system should be functioning normally prior to the MRI scan
- The pacemaker is reprogrammed to a special MRI mode immediately prior to the MR scan.

MR Scanner Limitations

The MRI scanner has to meet the following conditions:

- Use of a clinical MRI system with a cylindrical bore or elliptical bore and a static magnetic field strength of 1.5 Tesla.
- The slew rate of the MRI scanner's gradient fields should not exceed 200 T/m/s per axis.
- No additional local transmitting coils are used.

Restrictions during the MR Scan

The following conditions must be met during the MR scan:

- The mean specific absorption rate (SAR) for the whole body displayed by the MR scanner must not exceed 2.0 W/kg.
- The head absorption rate displayed by the MRI scanner must not exceed 3.2 W/kg.
- Emergency equipment for resuscitation must be kept at hand and properly certified staff must be readily available.
- The patient should be continuously monitored in an appropriate manner during the entire MR scan. Among others, the following parameters can be observed for this purpose:
    - Blood oxygen saturation
    - Blood pressure
    - ECG
- Adherence to the permissible positioning ranges (See Section 5). The isocenter of the high-frequency coil should not be below eye level or above the hip bone. In practice this means that the marker line of the laser light localizer, which is used for subsequent positioning of the patient within the MRI scanner, should not be set below eye level (lower edge of eye socket) and not above the hip bone (two fingers above the symphysis). These areas have to be adhered to during the MR scan.

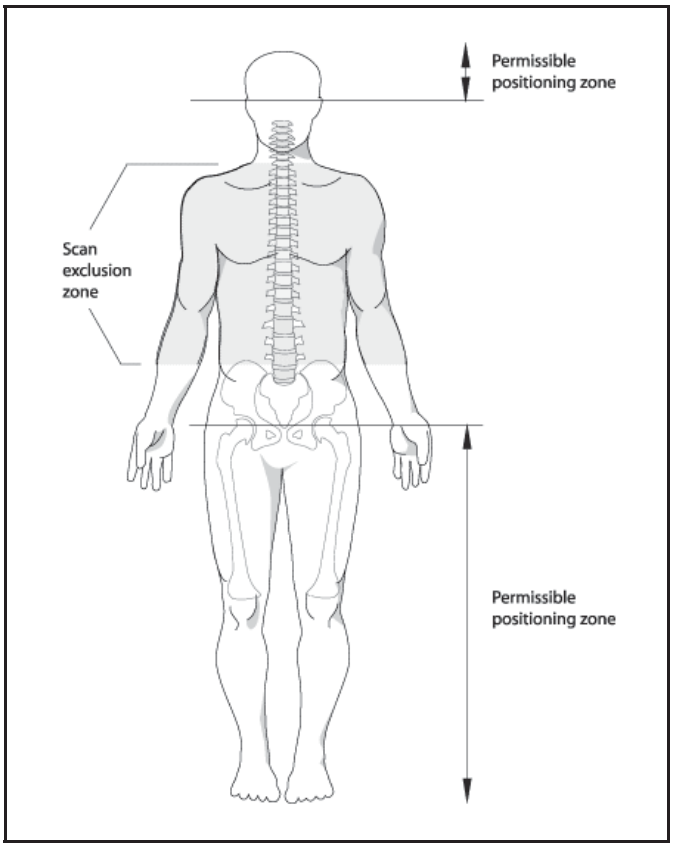
Post MR Scan Requirements

After the MR scan, the patient must undergo follow-up device interrogation. This is necessary for the patient's safety for two reasons:

- To reprogram the device back into the original pacing parameters.
- To assess the device system for any adverse effects caused by the MR scan

Permissible Positioning Zone and Scan Exclusion Zone

The first permissible positioning zone starts at the top of the skull and ends at eye level. The second permissible positioning zone starts at the hip bone level and ends at the patient's feet. The eyes and hip bone serve as the maximum allowed positioning marks for the isocenter of the MR scanner. These visible marks can be marked with a laser during MR scanner positioning. The figure below illustrates the permissible positioning zone and scan exclusion zone of the Entovis ProMRI system:



SUMMARY OF MR-RELATED LAB AND BENCH STUDIES

The following text and tables provide a concise summary of the non-clinical testing that was conducted in support of this submission. This information was developed based a summary provided by the sponsor, at FDA's request, during FDA's review of the submission.

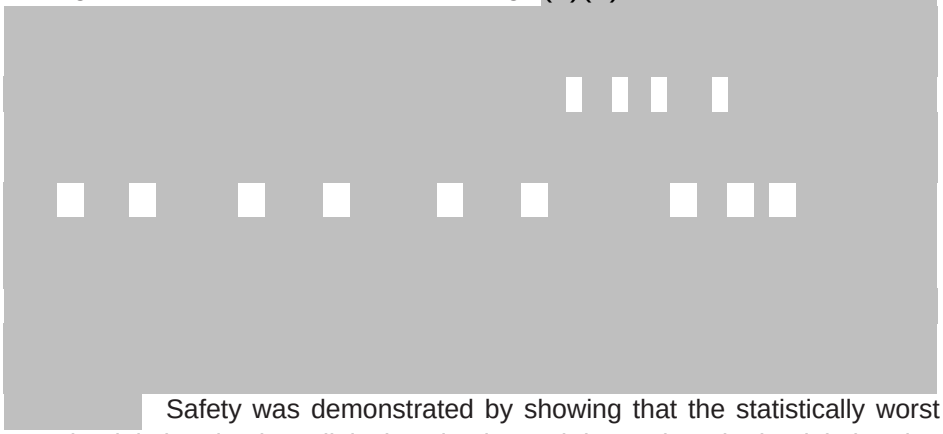
The FDA review team evaluated the non-clinical (bench, modeling, and animal study) data and analyses provided by the firm. FDA had previously reviewed many of these materials as part of G120226. FDA's remaining questions regarding these materials were discussed and resolved as part of Q131607. Additional information regarding these discussions is recorded in those files as well as the consult review memos from FDA's review team.

Extensive preclinical MRI testing was done in compliance with ISO/TS 10974:2012(E) "Assessment of the safety of magnetic resonance imaging for patients with an active implantable medical device". ISO/TS 10974:2012(E) lists twelve specific hazards that need to be evaluated. They are listed in the table below. Comprehensive preclinical MRI testing in compliance with ISO/TS 10974:2012(E) was completed for each of these hazards.

Potential Patient Hazards and Corresponding Test Requirements	
General Hazards to the Patient	**Test Requirement**

Potential Patient Hazards and Corresponding Test Requirements	
Heat	RF field-induced heating of the AIMD
	Gradient field-induced device heating
Vibration	Gradient field-induced vibration (malfunction)
	Gradient field-induced vibration (tissue damage)
Force	*B*0-induced force
Torque	*B*0-induced torque
Extrinsic electric potential	Gradient field-induced lead voltage
Rectification	RF field-induced rectified lead voltage
Malfunction	*B*0 field-induced device malfunction
	RF field-induced device malfunction
	Gradient field-induced device malfunction
	Combined fields- device malfunction

In compliance with ISO10974:2012(E), Preclinical test methods included in vitro (bench) testing, in vivo (animal) testing, and computer simulations (modeling). The following tables were provided by the sponsor and summarize the pre-clinical testing for the MRI-environment hazards.

RF field-induced heating of the Entovis Pulse Generator	
Field Interaction	Radio frequency
Mechanism and source of hazard	The conductive pacing leads act as “antennas”, picking up radiofrequency energy radiated from the MRI scanner body coil. A portion of this energy is then dissipated as heat in the cardiac tissue near the tip electrode.
Clinical Impact	Tissue heating near the tip electrode may result in thermal damage to the tissue, changes in pacing capture threshold, and, in extreme cases, loss of pacing therapy.
Evaluation method	The test was performed according to ISO/TS 10974: 2012 (E) §10. Biotronik used pacing capture threshold as a method to measure tissue damage due to RF-induced lead heating. (b)(4) TS/CCI  Safety was demonstrated by showing that the statistically worst case lead tip heating in a clinical setting is much lower than the lead tip heating that establishes a meaningful pacing capture threshold change in the canine model.
Results & Conclusions	The Entovis ProMRI pacing system modeling and in vivo evaluation demonstrate that the statistically worst case lead tip heating in a clinical setting is much lower than the lead tip heating that result in a meaningful pacing capture threshold change. The testing and modeling demonstrate the safety and effectiveness of the Entovis ProMRI pacing system in relation to the lead heating hazard.

Gradient field-induced device heating	
Field interaction	Gradient
Mechanism and source of hazard	The gradient field induces circulating electrical currents on conductive surfaces such as the pacemaker housing. This energy is then dissipated in the form of heat.
Clinical impact	Patient discomfort or damage to tissue in contact with the pacemaker housing.

Gradient field-induced device heating	
Evaluation method	This testing was performed according to ISO/TS 10974: 2012 (E) §11, IEC 60601-2-33: ed3.0, EN 45502-2-1:2003, ASTM F2182 – 11a, and ANSI PC69:2007. Heating of the housing was evaluated in vitro at the worst-case conditions for gradient magnetic field exposure allowed by the MR Conditions of Use specified in the labeling.
Results & **Conclusions**	The testing confirmed that at worst-case test conditions, there is acceptable heating of the pacemaker housing.

Gradient field-induced vibration (malfunction)	
Field interaction	Static and gradient
Mechanism and source of hazard	The gradient magnetic field induces time-varying currents in the conductive surfaces of the pacemaker. When these currents interact with the static magnet field it results in a time-varying force, causing the device to vibrate.
Clinical impact	MRI-induced vibration can affect internal pacemaker components and may result in pacemaker failure, leading to loss of pacing therapy and syncope.
Evaluation method	The test was performed according to ISO/TS 10974: 2012 (E) §12.3, and EN 45502-2-1:2003. Biotronik measured the worst case device vibration that could be observed during clinical MRI scans allowed by the MR Conditions for Use specified in the labeling. Vibration testing was then conducted at vibration stress levels well above the measured worst case vibration levels using a frequency range that spanned the gradient frequencies. Device functionality was monitored during and after the exposure. A post-test evaluation was performed to check for resets, state changes, and other damage to the pacemaker.
Results & **Conclusions**	The test results demonstrate that the Entovis ProMRI pacing system will deliver appropriate therapy during an MRI and that MRI exposure does not compromise subsequent operation, pacemaker reliability, or longevity. The testing demonstrates the safety and effectiveness of the Entovis ProMRI pacing system in relation to the gradient field induced vibration (malfunction) hazard.

Gradient field-induced vibration tissue damage	
Field interaction	Static and gradient
Mechanism and source of hazard	Gradient magnetic fields induce time-varying currents in the conductive surfaces of pacemaker components. When these currents interact with the static magnet field, it results in a time-varying force, causing the system to vibrate.
Clinical impact	MRI-induced vibration can cause discomfort and tissue damage.
Evaluation method	The test was performed according to ISO/TS 10974: 2012 (E) §12.5, EN 45502-2-1:2003, and IEC 60601-2-33. Biotronik measured the worst case device vibration that could be observed during clinical MRI scans during exposure to fields allowed by the MR Conditions for Use specified in the labeling.
Results & Conclusions	The in vitro evaluation showed that the worst case vibration forces are well below levels which might cause tissue damage. These results support the safety and effectiveness of the Biotronik Entovis ProMRI system with regard to tissue damage due to MRI-induced vibration.

***B*0-induced force**	
Field interaction	Static Field
Mechanism and source of hazard	The static magnetic field may move the pacemaker and/or leads if ferromagnetic or paramagnetic material is present.
Clinical impact	Tugging sensation, pacemaker dislodgement, or tissue injury at the implant location.
Evaluation method	The test was performed according to ISO/TS 10974: 2012 (E) §13 and ASTM F2052-06.
Results & **Conclusions**	The in vitro testing demonstrated that there is minimal MRI-induced force on the system. This testing supports the safety of the Entovis ProMRI Pacemaker system with regard to MRI-induced force hazards.

***B*0-induced torque**	
Field interaction	Static Field
Mechanism and source of hazard	The static magnetic field may rotate the pacemaker and leads if ferromagnetic or paramagnetic material is present in the pacemaker or leads.
Clinical impact	Tugging sensation, pacemaker dislodgement, or tissue injury at the implant location.
Evaluation method	The test was performed according to ISO/TS 10974: 2012 (E) §14 and ASTM F2213-06.
Results & **Conclusions**	The in vitro testing demonstrated that there is minimal MRI-induced torque on the system. This testing supports the safety of the Entovis ProMRI Pacemaker system with regard to MRI-induced torque hazards.

Gradient field-induced lead voltage	
Field interaction	Gradient field
Mechanism and source of hazard	The time-varying gradient magnetic fields will induce a time-varying voltage along the pacing leads.
Clinical impact	If the MRI-induced voltage pulses are large enough, they may directly stimulate the heart.
Evaluation method	The test was performed according to ISO/TS10974: 2012 (E) §16 Annex T, and EN 45502-2-1:2003. The test applied a sequence of pulse sequences to both the atrial and ventricular pacing leads and observed the equivalent charge induced by the waveform.
Results & Conclusions	The testing demonstrates the safety and effectiveness of the Entovis ProMRI pacing system in relation to the gradient field induced lead voltage hazard.

RF field-induced rectified lead voltage	
Field interaction	Radio frequency
Mechanism and source of hazard	The pacemaker circuitry connected to pacing leads may rectify the radiofrequency pulses.
Clinical impact	If the rectified voltages are large enough, it may directly stimulate the heart.
Evaluation method	The test was performed according to ISO/TS 10974: 2012 (E) §17 and §19, IEC 60601-2-33, EN 45502-2-1: 2003, and ANSI/AAMI PC69: 2007. The simulation framework described in the RF field-induced heating table was used to determine the worst case signal induced on the lead during an MRI scan. Rectification was measured during the direct injection of this worst case induced RF signal onto each contact of each lead port.
Results & Conclusions	The testing demonstrates the safety and effectiveness of the Entovis ProMRI pacing system in relation to the RF field induced rectified lead voltage hazard.

***B*0 field-induced device malfunction**	
Field interaction	Static Field
Mechanism and source of hazard	The static fields present in the MRI environment may adversely impact the pacemaker system.
Clinical impact	Loss of pacing therapy and syncope.
Evaluation Method	The test was performed according to ISO/TS 10974: 2012 (E) §18, and EN 45502-2-1:2003 The test devices were exposed to B0 field in a clinical scanner for at least one hour in each of the three orthogonal orientations. Device functionality was monitored during and after the exposure. A post-test was performed to check for resets, state changes, and other damage.
Results & **Conclusions**	The test results demonstrate that the Entovis ProMRI pacing system will deliver appropriate therapy during an MRI static field exposure and that MRI static field exposure does not compromise subsequent operation, pacemaker reliability, or longevity. The testing demonstrates the safety and effectiveness of the Entovis ProMRI pacing system in relation to the B0 static field induced malfunction hazard.

RF field-induced device malfunction	
Field interaction	Radio frequency
Mechanism and source of hazard	The radio frequency fields present in the MRI environment may adversely impact the operation of the pacemaker system.
Clinical impact	Loss of pacing therapy and syncope.
Evaluation Method	The test was performed according to ISO/TS10974: 2012 (E) §17 and §19, EN 45502-2-1: 2003, and ANSI/AAMI PC69: 2007. The simulation framework described in the RF field-induced heating table was used to determine the worst case signals induced on the leads during an MRI scan. This worst case signal was then directly injected into each contact on each lead port. Device functionality was monitored during and after the exposure. A post-test was performed to check for resets, state changes, and other damage.
Results & **Conclusions**	The test results demonstrate that the Entovis ProMRI pacing system will deliver appropriate therapy during an MRI's RF field exposure and that MRI RF exposure does not compromise subsequent operation, pacemaker reliability, or longevity. The testing demonstrates the safety and effectiveness of the Entovis ProMRI pacing system in relation to the radio frequency field induced malfunction hazard.

Gradient field-induced device malfunction	
Field interaction	Gradient
Mechanism and source of hazard	The gradient fields present in the MRI environment may adversely impact the operation of the pacemaker system.
Clinical impact	Loss of pacing therapy and syncope.
Evaluation Method	The test was performed according to ISO/TS 10974:2012 (E) §20.2 and §20.3, IEC 60601-2-33, EN 45502-2-1:2003, and ANSI/AAMI PC69: 2007. Biotronik exposed the system to a large number of gradient sequences (both injected and radiated) for several hundred hours. Device functionality was monitored during and after the exposure. A post-test evaluation was performed to check for resets, state changes, and other damage.

Gradient field-induced device malfunction	
Results & **Conclusions**	The test results demonstrate that the Entovis ProMRI pacing system will deliver appropriate therapy during an MRI and that MRI exposure does not compromise subsequent operation, pacemaker reliability, or longevity. The testing demonstrates the safety and effectiveness of the Entovis ProMRI pacing system in relation to the gradient field induced malfunction hazard.

Combined fields - device malfunction	
Field interaction	Static, Gradient, and Radio frequency
Mechanism and source of hazard	The combined effects of the static, gradient, and radio frequency fields present in the MRI environment may adversely impact the operation of the pacemaker system.
Clinical impact	Loss of pacing therapy and syncope.
Evaluation Method	The test was performed according to ISO/TS10974: 2012 (E) §21, and EN 45502-2-1:2013. The test was performed by exposing the Entovis system to various scanner sequences and resultant field distributions in the MR environment while monitoring the pulse generator behavior. Measurements were made with a variety of lead paths, pacemaker modes, and positions in the phantom. Device functionality was checked after the exposure. A post-test evaluation was performed to check for resets, state changes, and other damage.
Results & **Conclusions**	The test results demonstrate that the Entovis ProMRI pacing system will deliver appropriate therapy during an MRI and that MRI exposure does not compromise subsequent operation, pacemaker reliability, or longevity. The testing demonstrates the safety and effectiveness of the Entovis ProMRI pacing system in relation to the combined static, gradient, and radio frequency hazard.

OVERALL APPROACH TO EVALUATING RF HEATING

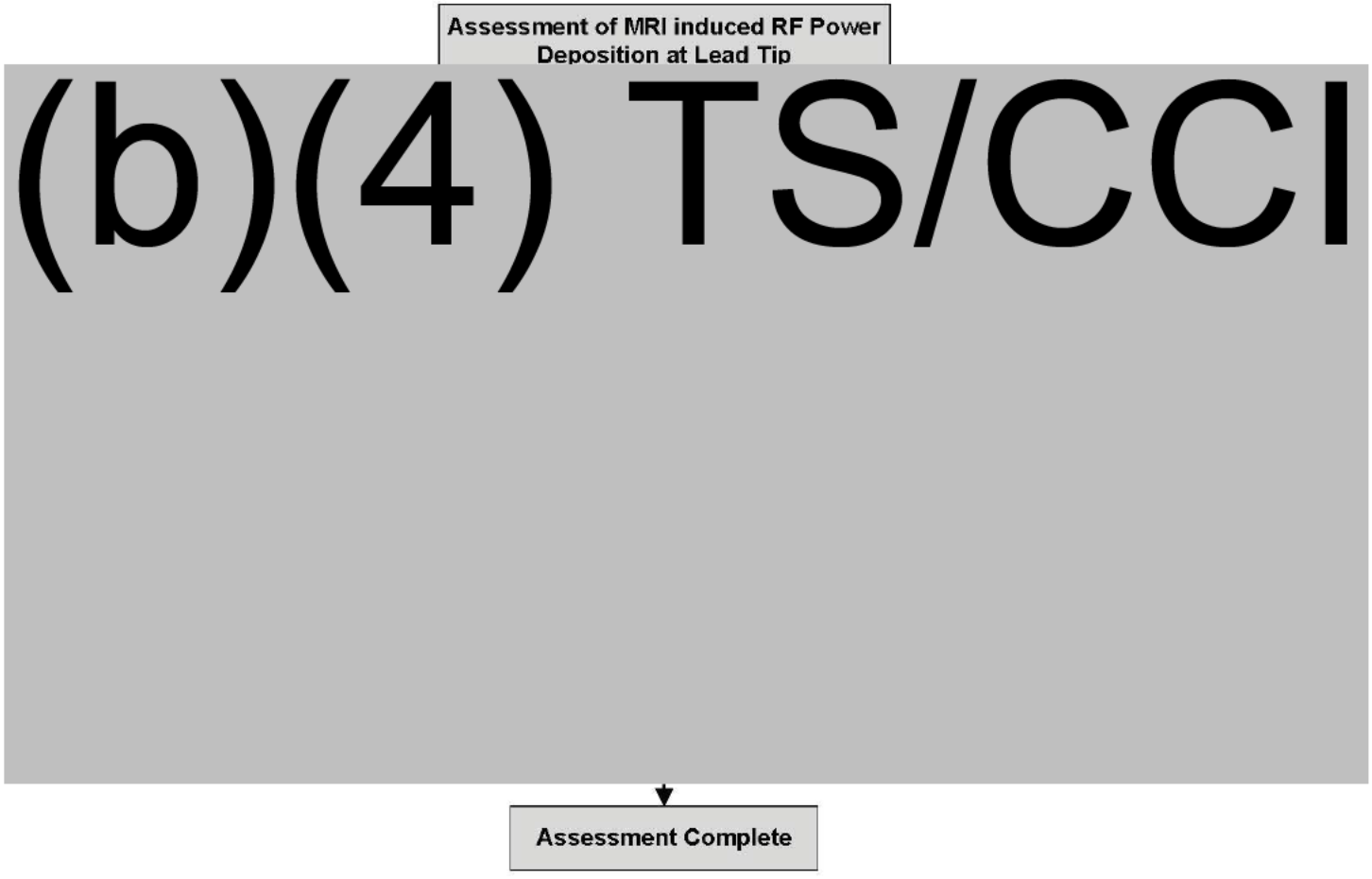
The firm developed an overall RF heating validation approach that was submitted to FDA on April 8, 2011 in pre-IDE supplement I100712/S001 and discussed during the June 14, 2011 FDA face-to-face meeting. This approach was based on firm's previous Pre-IDE experiences, the firm's understanding of Medtronic's Revo MRI SureScan pacing system testing (P090013, dated February 8, 2011), and the firm's system risk analysis. The approach was developed to demonstrate in a clinically relevant manner that the worst-case deposited energy, as predicted by modeling, has no significant physiological impact with regard to pacing efficacy or patient safety.

FDA met with the firm multiple times, using the Pre-IDE and Pre-Submission meeting process, in order to provide constructive feedback on their overall approach to evaluating the potential adverse impact of MR scans on the implanted pacemaker system and patient.

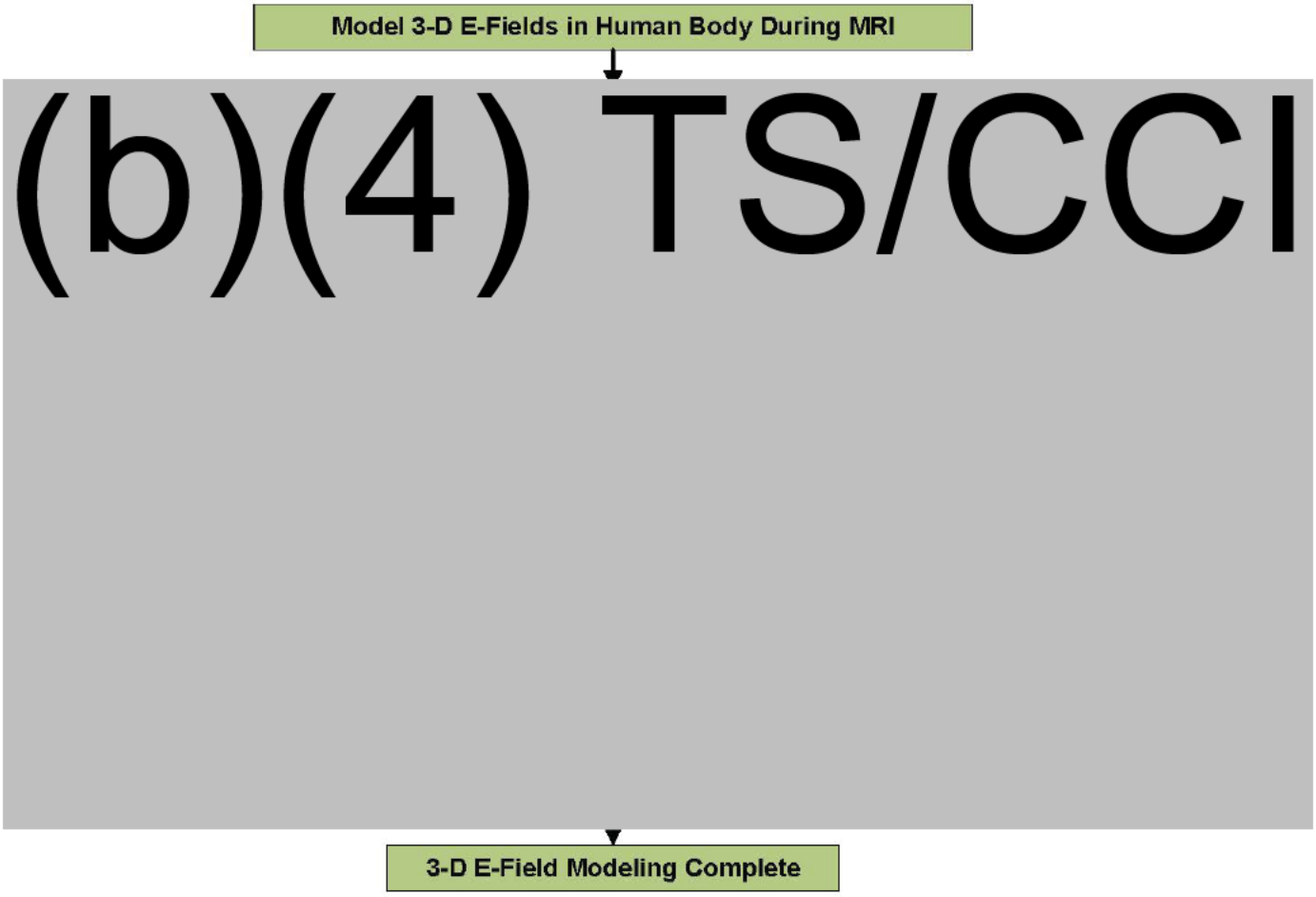
BIOTRONIK's overall approach was designed to be in alignment with the Joint Working Group's International Technical Specification for ISO/TS 10974: 2012 (E) and includes the following:

(b)(4) TS/CCI

The firm provided a flowchart that summarizes the overall approach for RF heating validation.



Computer simulations were used to calculate incident E-fields for a broad patient population and wide range of clinical scenarios. This modeling approach is necessary for cases where interactions between the MRI environment and the human body and implanted pacing system are too complex to be evaluated using only in vitro or in vivo methods. The firm provided a flowchart that summarizes the overall approach for modeling.



The firm provided additional a thorough description of the overall modeling and evaluation plan in their submission. As previously stated, FDA reviewed the firm's approach as part of our evaluation of this PMA Supplement as well as multiple previous submissions.

SUMMARY OF CLINICAL EXPERIENCE

Background for Supporting Clinical Studies

The ProMRI Study and the ProMRI AFFIRM Study were prospective, single-arm, non-randomized, multi-center, studies designed to demonstrate the clinical safety of the ProMRI Pacemaker System when used under specific MRI conditions.

On July 20, 2011, a pre-IDE supplement was submitted to FDA following their recommendation to review the final clinical protocol that was originally planned to be conducted outside the U.S. (OUS). FDA's pre-

IDE feedback was incorporated into the ProMRI AFFIRM study. This ProMRI AFFIRM study was initiated in February 2012, however, due to slow enrollment in the OUS study, the firm decided to submit an IDE application to FDA.

On October 3, 2012, the firm submitted an Original IDE for the ProMRI study to evaluate the safety and effectiveness of the Entovis ProMRI system when used under specific MRI conditions (G120226). FDA provided an IDE approval with conditions in correspondence dated December 21, 2012. Due to slow enrollment in the US study, the firm decided to pool the data from the OUS ProMRI AFFIRM and the US ProMRI studies. This resulting report is intended to support a PMA Supplement requesting FDA approval of MRI conditions for the firm pacing systems as outlined herein.

The firm, Biotronik, was the sponsor of both the OUS ProMRI AFFIRM study and the US ProMRI study.

Introduction

The ProMRI Study and the ProMRI AFFIRM Study are prospective, single-arm, non-randomized, multi-center, studies designed to demonstrate the clinical safety of the ProMRI Pacemaker System when used under specific magnetic resonance imaging (MRI) conditions. The ProMRI AFFIRM study was conducted outside the US and the ProMRI study was conducted in the US. Both studies have the same clinical study design and data from the two studies was pooled for endpoint analysis.

Primary Objectives

This clinical investigation was designed to demonstrate the clinical safety of the ProMRI Pacemaker System when used under specific magnetic resonance imaging (MRI) conditions. The investigation included 5 primary endpoints, which condense into 3 main objectives:

- Primary Endpoint 1 – Evaluation of serious adverse device effect (SADE) rate related to the implanted pacing system and MRI procedure
- Primary Endpoints 2 & 3 – Evaluation of atrial and ventricular lead pacing threshold increases
- Primary Endpoints 4 & 5 – Evaluation of P-wave and R-wave sensing attenuation

Methods

These studies enrolled subjects implanted with an Entovis family pacemaker (SR-T, DR-T) and one or two Setrox S 53 or 60 leads, and were willing to undergo an MRI scan.

The patients selected for participation were from the investigator's general patient population meeting the indications for use of the Entovis family pacemaker system. To qualify for enrollment, subjects were required to have measurable pacing thresholds ≤ 2.0 V @ 0.4 ms and could not be implanted with other non-MRI compatible devices. Patients received a baseline evaluation at least 7 days prior to the MRI procedure, at which time the pacemaker was tested and programmed to an MRI mode before the MRI, then tested and reprogramed to the original pacing mode post-MRI. The study required an MRI position exclusion zone: the isocenter of the scanner could not be positioned below eye level or above trochanter level.

Patients were enrolled post-implant, underwent an MRI procedure and testing, and were followed at one and three months post-MRI. During follow-up visits, a device interrogation was completed and the investigator determined if the MRI scan had any long-term effects on the function of the pacemaker system.

Results

The study involved 229 enrolled patients with a cumulative implant duration at baseline and MRI procedure of 51.8 years (average implant duration of 0.23 ± 0.22 years) and 66.4 years (average implant duration of 0.29 ± 0.22), respectively. The investigation was conducted at 25 centers in the US and 12 centers in Europe, totaling 37 centers with at least one provisional enrollment. The patient follow-up compliance rate was 99.5% out of 440 required follow-ups. Endpoint data is provided for the Per Protocol (PP) and Intention-to-treat (ITT) Populations. At the time of data analysis, 229 patients had been programmed into MRI mode and 226 had completed their 1 month follow-up. The average subject is a 71 year old male who weighs 185 pounds and is 68 inches in height.

Primary Endpoint 1

The purpose of Primary Endpoint 1 was to evaluate the rate of Serious Adverse Device Effects related or possibly related to the implanted pacing system and the MRI procedure. Only SADEs that were pacing system and MRI related or possibly related, as adjudicated by the independent Data Monitoring Committee, were taken into account for calculation of the SADE rate.

Analysis

The Data Monitoring Committee (DMC) adjudicated 28 events reported by the investigators. No events were adjudicated as related or possibly related to the implanted pacing system, resulting in an SADE-free rate of 100.0% (229/229), $p < 0.001$, 95% CI: (98.4%, 100.0%).

Two events (one serious and one non-serious) were adjudicated as possibly related to the MRI procedure. Accounting for the one serious adverse event (SAE) not related to the implanted pacing system but possibly related to the MRI procedure, the SAE-free rate was 99.6% (228/229), $p < 0.001$, 95% CI: (97.6%, 100.0%). Accounting for both adverse events (AEs) possibly related to the MRI procedure, the AE-free rate was 99.1% (227/229), $p < 0.001$, 95% CI: (96.9%, 99.9%).

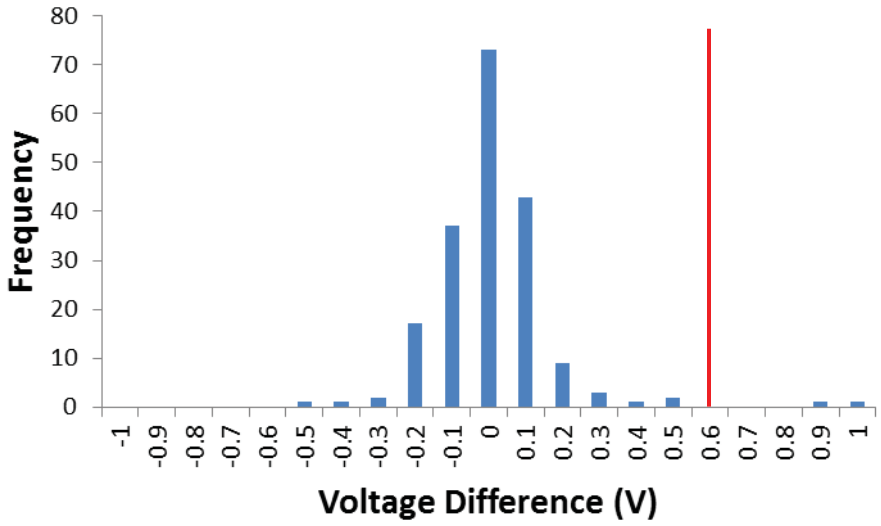
Primary Endpoints 2 & 3

The purpose of Primary Endpoints 2 and 3 was to evaluate the percentage of atrial and ventricular pacing leads with a pacing threshold increase between the pre-MRI and 1-month post-MRI follow-up. The threshold behavior of the lead is defined as a success if the increase is not larger than 0.5 V. The tables and figures below display the differences in atrial and ventricular pacing thresholds.

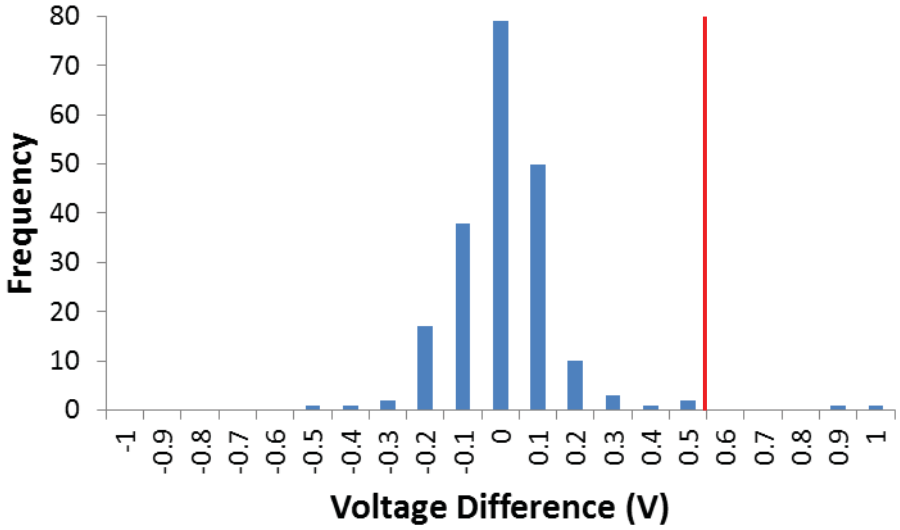
Atrial Pacing Threshold

	Results	P-value*
Intention-to-treat (ITT): Includes Values Imputed from Home Monitoring (N=206)		
Difference in Atrial Pacing Threshold (V)		
Mean ± SD (N)	0.01 ± 0.16	
Minimum, Median, Maximum	(b)(4) TS/CCI	
Leads Meeting Success Criteria (%)	204 (99.0%)	P = 0.002
95% Confidence Interval	(96.5%, 99.9%)	
Per Protocol (N=191)		
Difference in Atrial Pacing Threshold (V)		
Mean ± SD (N)	0.01 ± 0.16	
Minimum, Median, Maximum	(b)(4) TS/CCI	
Leads Meeting Success Criteria (%)	189 (99.0%)	P = 0.003
95% Confidence Interval	(96.3%, 99.9%)	

Histogram of PPP Atrial Pacing Threshold Differences (One-Month – Pre-MRI)



Histogram of ITT Atrial Pacing Threshold Differences (One-Month – Pre-MRI)



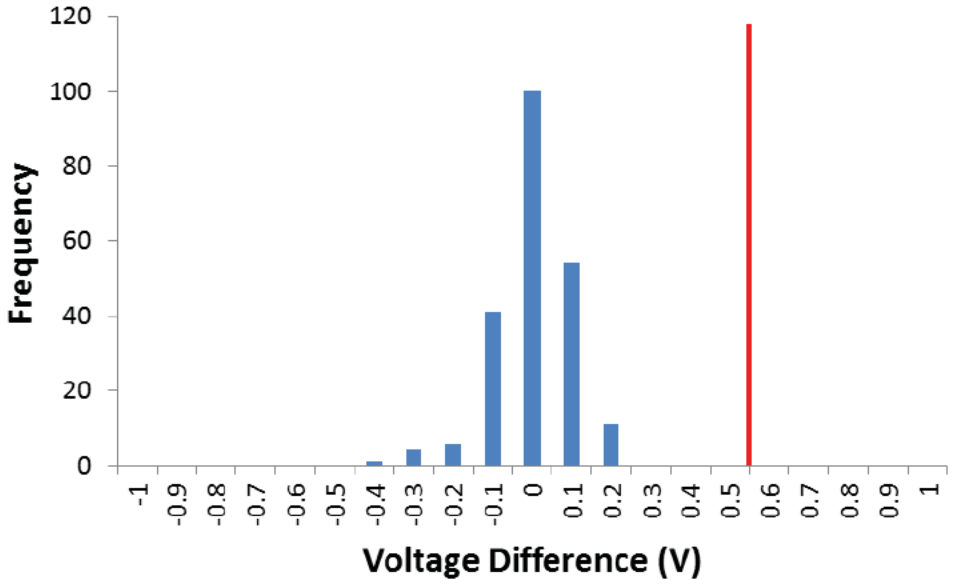
Atrial Analysis

The mean threshold increase of both populations was 0.01 ± 0.16. Of 191 total subjects in the PP population and the 206 total subjects with data in the ITT population, 189 (99.0%, p = 0.003) and 204 (99.0%, p = 0.002) had a change in atrial pacing threshold of less than or equal to 0.5V between one-month post-MRI and pre-MRI, respectively. A rejection of the null hypothesis indicates that the proportion of atrial pacing threshold success is greater than 95% and Primary Endpoint 2 is met.

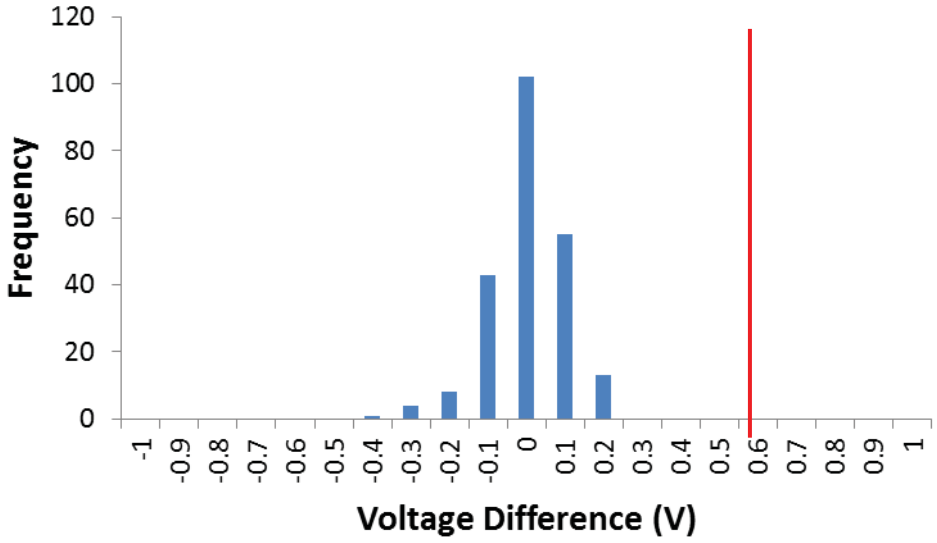
Ventricular Pacing Threshold

	Results	P-value*
Intention-to-treat (ITT): Includes Values Imputed from Home Monitoring (N=226)		
Difference in Ventricular Pacing Threshold (V)		
Mean ± SD (N)	0.00 ± 0.10	
Minimum, Median, Maximum	(b)(4) TS/CCI	
Leads Meeting Success Criteria (%)	226 (100.0%)	P <0.001
95% Confidence Interval	(98.4%, 100.0%)	
Per Protocol (N=217)		
Difference in Ventricular Pacing Threshold (V)		
Mean ± SD (N)	0.00 ± 0.10	
Minimum, Median, Maximum	(b)(4) TS/CCI	
Leads Meeting Success Criteria (%)	217 (100.0%)	P < 0.001
95% Confidence Interval	(98.3%, 100.0%)	

Histogram of PPP Ventricular Pacing Threshold Differences (One-Month – Pre-MRI)



Histogram of ITT Ventricular Pacing Threshold Differences (One-Month – Pre-MRI)



Ventricular Analysis

The mean threshold increase of both populations was 0.00 ± 0.10. Of 217 total subjects in the PP population and the 226 total subjects with data in the ITT population, all had a change in ventricular pacing threshold of less than or equal to 0.5V between 1-month post-MRI and pre-MRI, respectively. A rejection of the null hypothesis (p-values: PP – <0.001 and ITT – <0.001) indicates that the proportion of ventricular pacing threshold success is greater than 95% and Primary Endpoint 3 is met.

Primary Endpoints 4 & 5

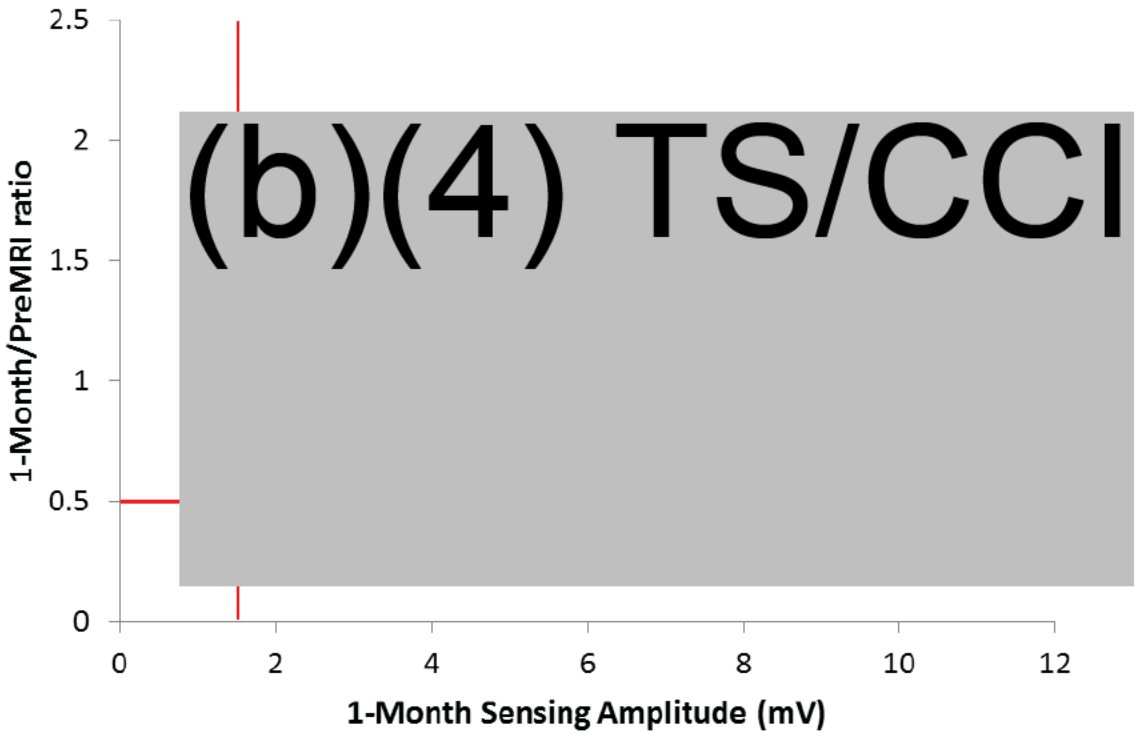
The purpose of Primary Endpoints 4 and 5 was to evaluate the percentage of subjects who experienced P-wave and R-wave attenuation between the pre-MRI and 1-month post-MRI follow-up. Sensing amplitude attenuation was defined as either a P-wave or R-wave amplitude decrease (between pre-MRI and one month follow-up) exceeding 50% or an amplitude at the one month follow-up of less than 1.5 mV and 5.0 mV in the atrium and ventricle, respectively. The tables and figures below display differences in atrial and ventricular sensing amplitudes over this period of time, the per protocol (PP) atrial sensing amplitude ratios with endpoint boundary conditions, and the intention-to-treat (ITT) sensing amplitude ratios with endpoint boundary conditions.

P-Wave Sensing Attenuation

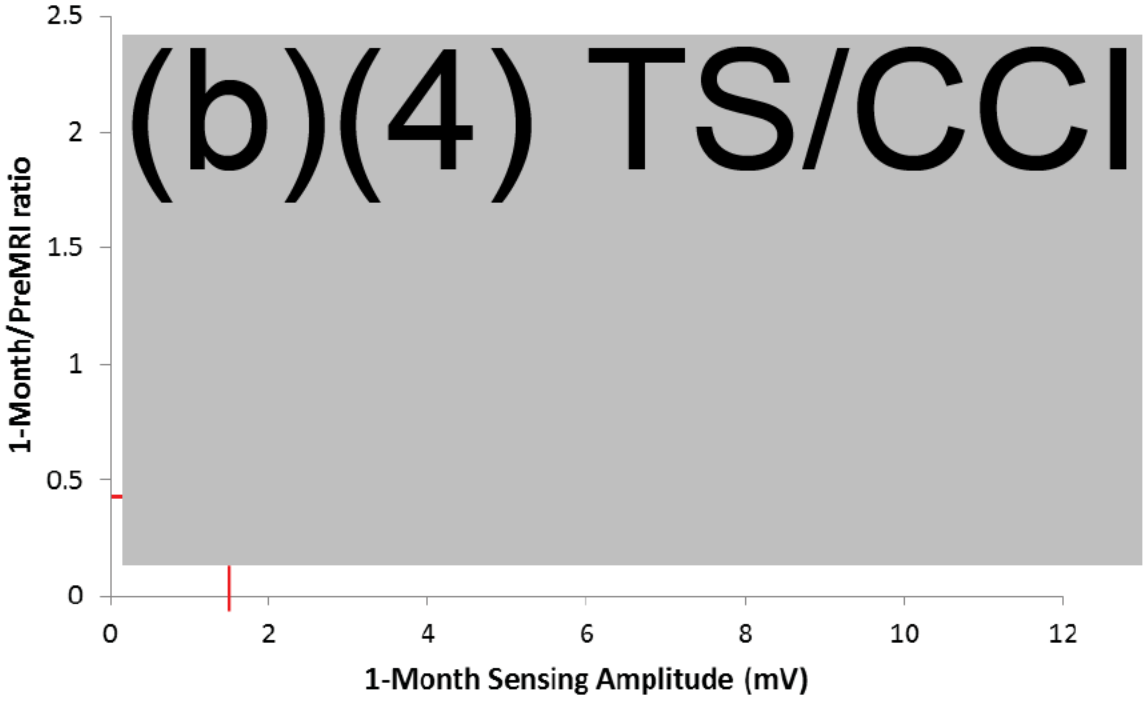
	Results	P-value*
Intention-to-treat (ITT): Includes Values Imputed from Home Monitoring (N=206)		
Difference in P-wave Amplitude (mV)		
Mean ± SD (N)	0.00 ± 0.91	
Minimum, Median, Maximum	(b)(4) TS/CCI	
Leads Meeting Success Criteria (%)	203 (98.5%)	P <0.001
95% Confidence Interval	(95.8%, 99.7%)	
Per Protocol (N=168)		
Difference in P-wave Amplitude m(V)		
Mean ± SD (N)	0.04 ± 0.91	
Minimum, Median, Maximum	(b)(4) TS/CCI	
Leads Meeting Success Criteria (%)	167 (99.4%)	P < 0.001
95% Confidence Interval	(96.7%, 100.0%)	

*Exact binomial test (1-sided) for comparison to 90%

Atrial PPP Sensing Amplitude Ratio with Boundary Conditions



Atrial ITT Sensing Amplitude Ratio with Boundary Conditions



Atrial Analysis

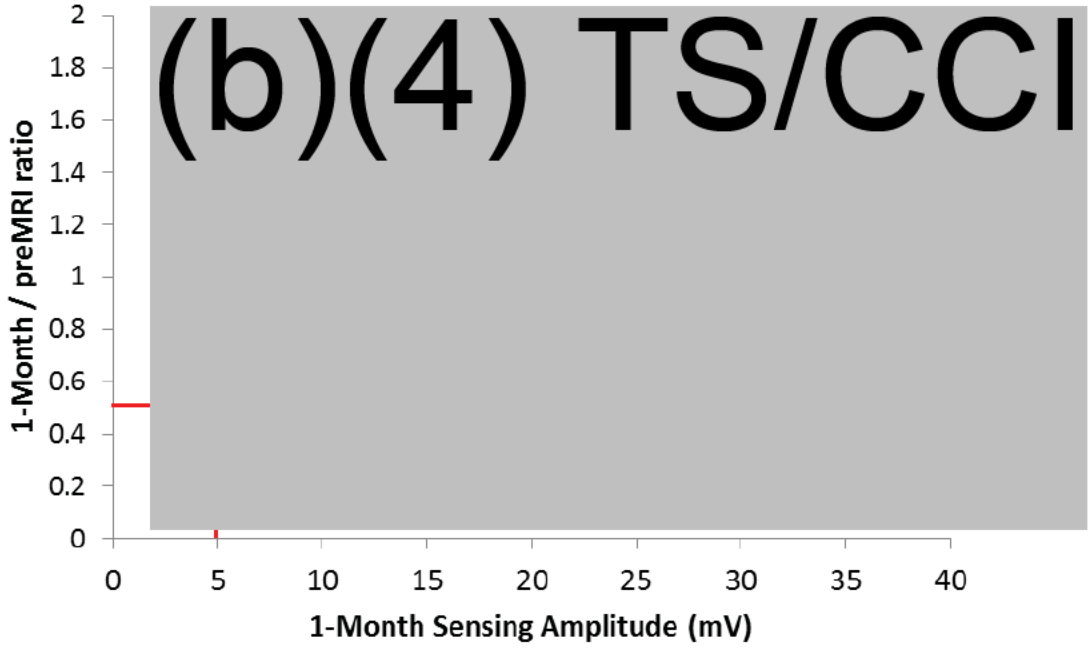
Of 168 total subjects in the PP population and 206 total subjects with data in the ITT population, 167 (99.4%, $p < 0.001$) and 203 (98.5%, $p < 0.001$) met the endpoint for attenuation-free P-wave sensing, respectively. A rejection of the null hypothesis indicates that the P-wave attenuation free rate is greater than 90% and Primary Endpoint 4 is met.

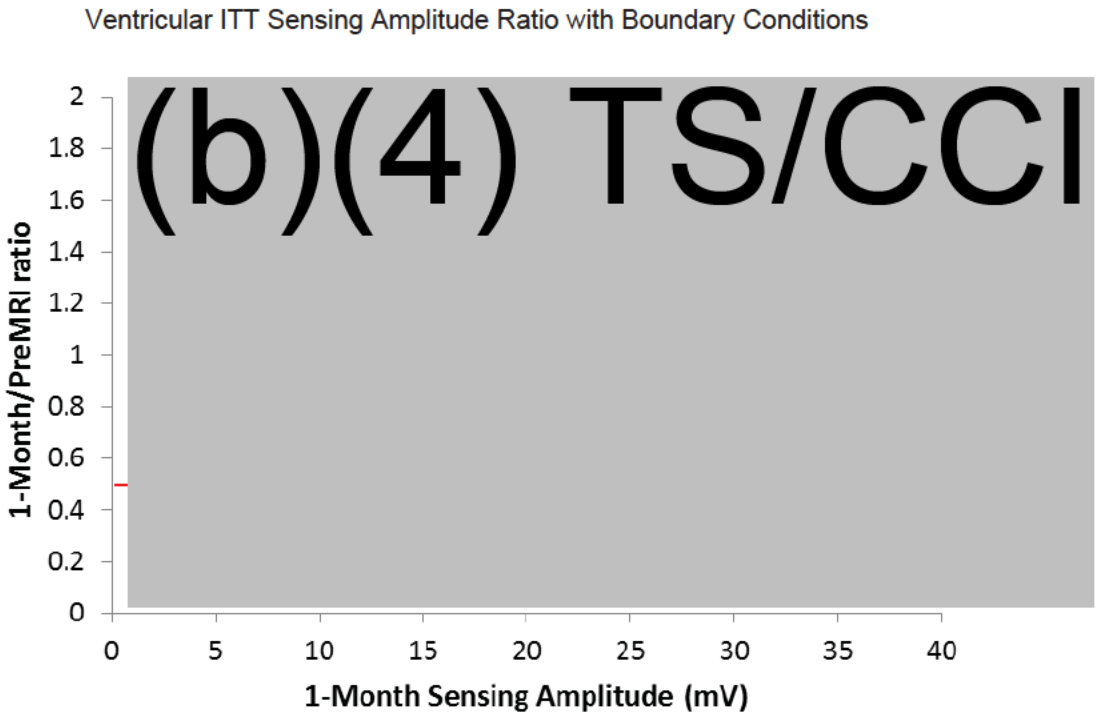
R-Wave Sensing Attenuation

	Results	P-value*
Intention-to-treat (ITT): Includes Values Imputed from Home Monitoring (N=224)		
Difference in R-wave Amplitude (mV)		
Mean ± SD (N)	0.13 ± 1.76	
Minimum, Median, Maximum	(b)(4) TS/CCI	
Leads Meeting Success Criteria (%)	222 (99.1%)	P <0.001
95% Confidence Interval	(96.8%, 99.9%)	
Per Protocol (N=194)		
Difference in R-wave Amplitude m(V)		
Mean ± SD (N)	0.08 ± 1.65	
Minimum, Median, Maximum	(b)(4) TS/CCI	
Leads Meeting Success Criteria (%)	193 (99.5%)	P < 0.001
95% Confidence Interval	(97.2%, 100.0%)	

*Exact binomial test (1-sided) for comparison to 90%

Ventricular PPP Sensing Amplitude Ratio with Boundary Conditions





Ventricular Analysis

Of the 194 subjects in the PP population and 224 subjects with data in the ITT population, 193 (99.5%, $p < 0.001$) and 222 (99.1%, $p < 0.001$) met the endpoint for attenuation-free R-wave sensing, respectively. A rejection of the null hypothesis indicates that both the R-wave attenuation free rate is greater than 90% and Primary Endpoint 5 was met.

Observed Adverse Events

The US ProMRI and OUS ProMRI AFFIRM pooled clinical study data set included 229 enrolled subjects who were programmed into MRI mode with a cumulative number of Subject-Years since Baseline of 76.41.

Adverse events were classified as serious or non-serious. Serious adverse events were defined as events that resulted in a life-threatening illness or injury, resulted in permanent impairment of body structure or function, required in-patient hospitalization, resulted in medical or surgical intervention to prevent life threatening illness or permanent impairment, or led to fetal complications.

Of the 123 adverse events (AEs) reported, there have been 27 serious adverse events (SAEs) in 22 subjects and 96 non-serious adverse events in 67 subjects. A Data Monitoring Committee adjudicated all SAEs and none were found to be related or possibly related to the pacemaker system and the MRI procedure. Two events were adjudicated as possibly related to the MRI procedure.

Summary of Serious Adverse Events

SAE Category	Subjects with SAE (n)	% Subjects with SAE	Number of SAEs	SAEs per Subject-Year
Angina	2	0.9%	2	0.026
Arrhythmia	2	0.9%	2	0.026
Arterial Stenosis	2	0.9%	2	0.026
CAD	3	1.3%	3	0.039
Gastrointestinal	1	0.4%	1	0.013
Infection	2	0.9%	2	0.026
MI	1	0.4%	1	0.013
Mild to moderate post-operative risks	2	0.9%	2	0.026
Musculoskeletal	2	0.9%	3	0.039
Respiratory	1	0.4%	1	0.013
Seizure and Hyperglycemia	1	0.4%	1	0.013
Spinal Stenosis	1	0.4%	1	0.013
Stroke	1	0.4%	1	0.013
Syncope/Pre-Syncope	3	1.3%	5	0.065
Total	**22**	**9.6%**	**27**	**0.353**

Number of Enrolled Subjects = 229, Number of Subject-Years since Enrollment= 76.41

Summary of Non-Serious Adverse Events

AE Category	Subjects with AE (n)	% Subjects with AE	Number of AEs	AEs per Subject-Year
Angina	2	0.9%	2	0.026
Arrhythmia	13	5.7%	14	0.183
CAD	2	0.9%	2	0.026
Cancer	2	0.9%	2	0.026
Dermatological Condition	1	0.4%	1	0.013
Fatigue	2	0.9%	2	0.026
Gastrointestinal	5	2.2%	5	0.065
Gout	1	0.4%	1	0.013
Increased Threshold	1	0.4%	1	0.013
Influenza	2	0.9%	2	0.026
MRI Incidental Finding	17	7.4%	17	0.222
MRI Procedure Discomfort	9	3.9%	9	0.118
Medication Related	1	0.4%	1	0.013
Mild to moderate post-operative risks	1	0.4%	1	0.013

AE Category	Subjects with AE (n)	% Subjects with AE	Number of AEs	AEs per Subject-Year
Musculoskeletal	10	4.4%	10	0.131
Other	16	7.0%	17	0.222
Respiratory	2	0.9%	2	0.026
Syncope/Pre-Syncope	6	2.6%	6	0.079
Undersensing	1	0.4%	1	0.013
Total	**67**	**29.3%**	**96**	**1.256**

Number of Enrolled Subjects = 229, Number of Subject-Years since Enrollment= 76.41

Conclusions

The ProMRI and ProMRI AFFIRM studies were designed to demonstrate the clinical safety of the ProMRI Pacemaker System when used under specific magnetic resonance imaging (MRI) conditions. A total of 229 (128 US and 101 OUS) subjects were enrolled at 34 sites (23 US and 11 OUS) as of November 18, 2013, the date ProMRI® US closed enrollment.

Overall Results

- No SADEs related or possibly to the implanted pacing system and the MRI procedure were reported in the study. The DMC adjudicated 28 events that were reported by the investigators. None were adjudicated as related or possibly to the implanted pacing system and the MRI procedure, resulting in a SADE-free rate of 100% (229/229), $p < 0.001$, 95% CI: (98.4%, 100.0%). A rejection of the null hypothesis indicates that the SADE-free rate possibly related to the implanted pacing system and the MRI procedure is less than or equal to 90% at 1 month post-MRI and the endpoint is met.

- Of 191 per protocol (PP) and 206 intention-to-treat (ITT) subjects, 189 (99.0%) and 204 (99.0%) had a change in atrial pacing threshold of less than or equal to 0.5V between one-month post-MRI and pre-MRI, respectively, resulting in a PP p-value of 0.003, 95% CI: (96.3%, 99.9%) and an ITT p-value of 0.002, 95% CI: (96.5%, 99.9%). A rejection of the null hypothesis indicates that the proportion of atrial pacing threshold success is greater than 95% and the endpoint is met.

- Of 217 per protocol (PP) and 226 intention-to-treat (ITT) subjects, all had a change in ventricular pacing threshold of less than or equal to 0.5V between one-Month post-MRI and pre-MRI resulting in a PP p-value of < 0.001, 95% CI: (98.3%, 100.0%) and an ITT p-value of < 0.001, 95% CI: (98.4%, 100.0%). A rejection of the null hypothesis indicates that the proportion of ventricular pacing threshold success is greater than 95% and the endpoint is met.

- Of 168 per protocol (PP) and 206 intention-to-treat (ITT) subjects, 167 (99.4%) and 203 (98.5%) met the endpoint for attenuation-free P-wave sensing, respectively, resulting in a PP p-value of < 0.001, 95% CI: (96.7%, 100.0%) and an ITT p-value of < 0.001, 95% CI: (95.8%, 99.7%). A rejection of the null hypothesis indicates that the P-wave attenuation free rate is greater than 90% and the endpoint is met.

- Of 194 per protocol (PP) and 224 intention-to-treat (ITT) subjects, 193 (99.5%) and 222 (99.1%) met the endpoint for attenuation-free R-wave sensing, respectively, resulting in a PP p-value of < 0.001, 95% CI: (97.2%, 100.0%) and an ITT p-value of < 0.001, 95% CI: (96.8%, 99.9%). A rejection of the null hypothesis indicates that the R-wave attenuation free rate is greater than 90% and the endpoint is met.

All five Primary Endpoints were met. The data received and analyzed demonstrates and supports the clinical safety and efficacy of the ProMRI Pacemaker System when used under specific MRI conditions.

The FDA review team evaluated the data and analyses that were presented in the PMA Supplement as well as the firm's additional interactive responses. FDA questions and concerns were addressed during the review of the file, and the clinical data and analyses provide confirmatory data, supporting a reasonable assurance of safety and effectiveness of the pacemaker system.

ADDITIONAL LEAD MEASUREMENT DATA FROM HOME MONITORING

The Entovis pulse generators include the capability to collect and store daily lead measurements as part of the Home Monitoring feature. FDA discussed this capability with the firm as part of the Pre-Submission process and suggested using this feature to capture additional supporting data, evaluating the impact of MR scans in the 30-days between the MR scan and the scheduled 1-month follow-up.

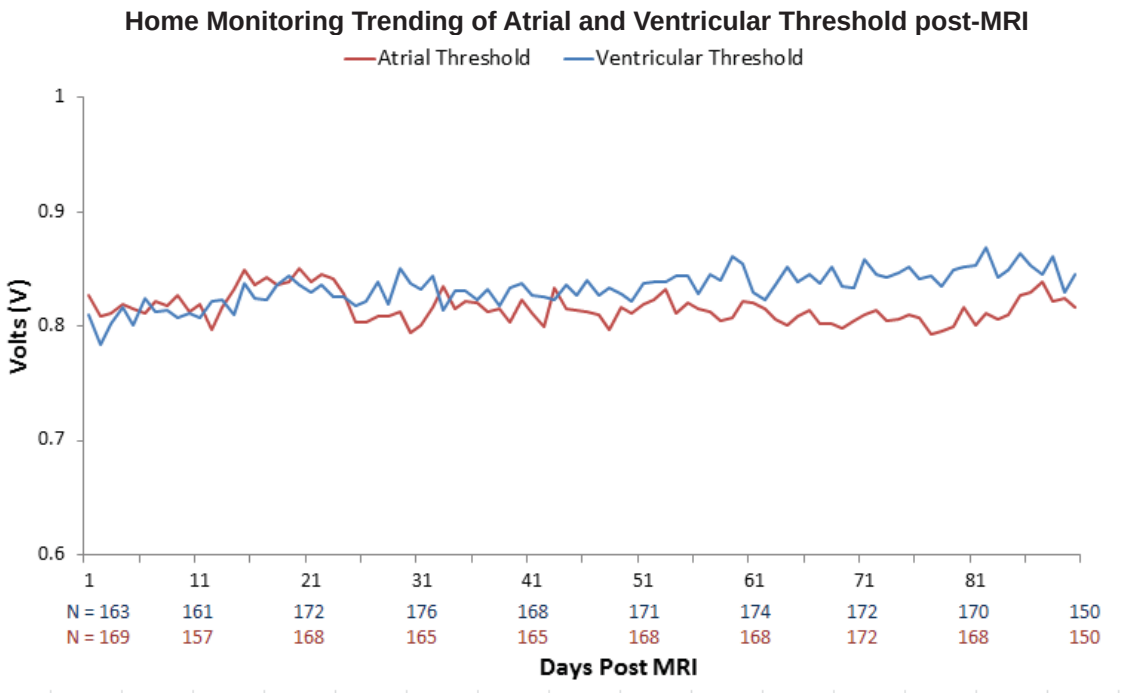
The firm provided this trending data in the original clinical report, which is summarized below.

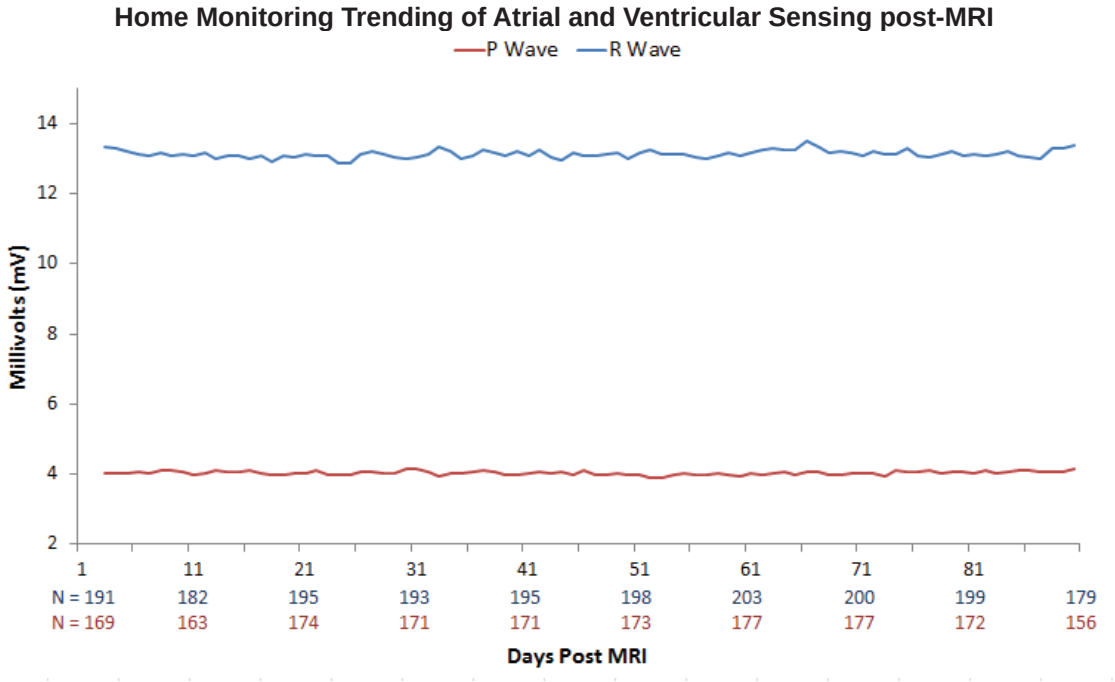
Following the MRI procedure, a Home Monitoring trend of the subject data was obtained over a period of 3 months. This will enable the monitoring of any long-term effects related to the clinical safety of the pacemaker system that result from the MRI scan. Of relevance is the daily monitoring and recording of the subject's pacing threshold changes, changes in P- and R-wave sensing and changes in the pacing impedance.

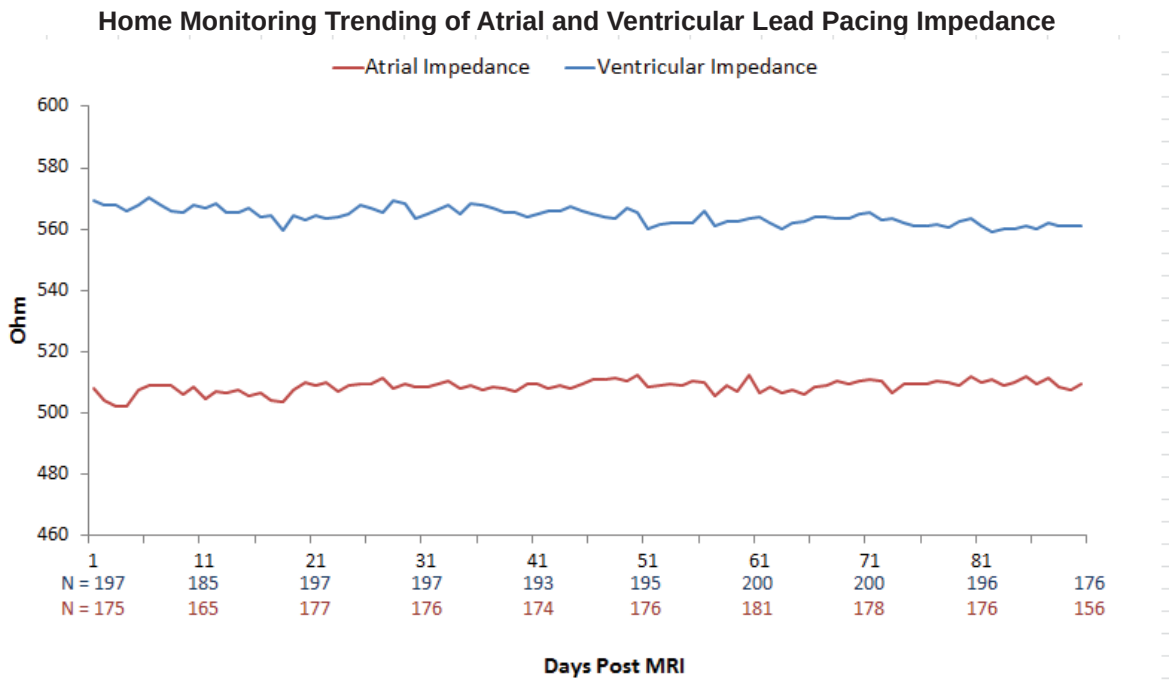
In this way, the long term effects of MRI were determined on a subject-specific basis. Mean pacing threshold, P- and R-wave sensing and pacing impedance for all subjects was calculated, to determine a general effect trend. Although all subjects were equipped with Home Monitoring, there were be gaps in a subject's daily Home Monitoring transmission due to the subjects' proximity to the CardioMessenger or being out of a GSM service area.

Data for pacing capture threshold collected automatically by the device as part of daily trend data collection with Home Monitoring is included with this report and will be included with the Final Report.

The figures display the averaged atrial and ventricular threshold, sensing, and pacing impedance per day post-MRI. The number of transmitted values at various time points is provided.


Home Monitoring Trending of Atrial and Ventricular Threshold post-MRI
Atrial Threshold
Ventricular Threshold
Volts (V)
1
0.9
0.8
0.7
0.6
1 11 21 31 41 51 61 71 81
N = 163 161 172 176 168 171 174 172 170 150
N = 169 157 168 165 165 168 168 172 168 150
Days Post MRI


Home Monitoring Trending of Atrial and Ventricular Sensing post-MRI
P Wave
R Wave
Millivolts (mV)
14
12
10
8
6
4
2
1 11 21 31 41 51 61 71 81
N = 191 182 195 193 195 198 203 200 199 179
N = 169 163 174 171 171 173 177 177 172 156
Days Post MRI

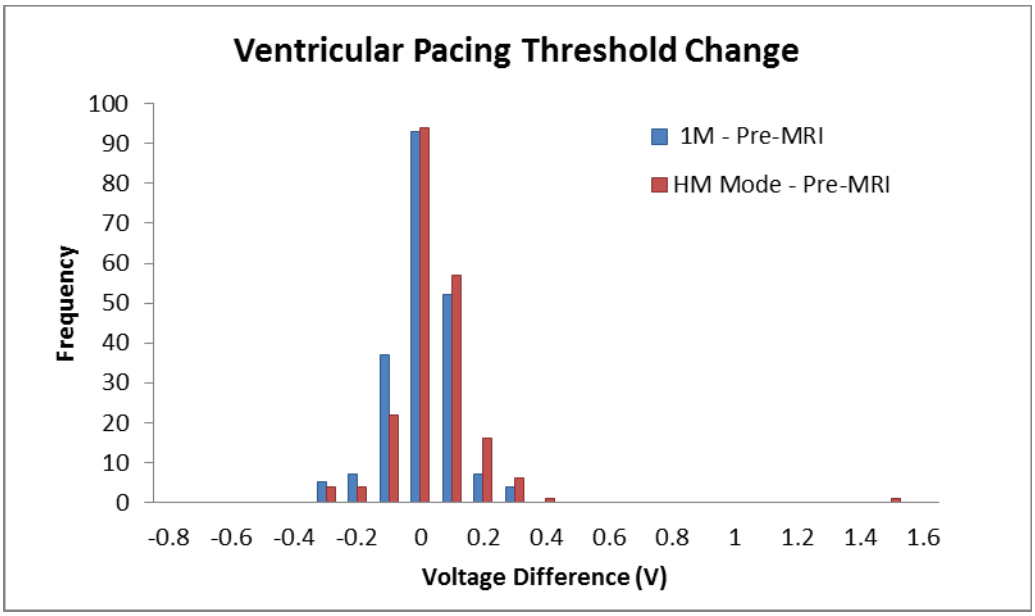


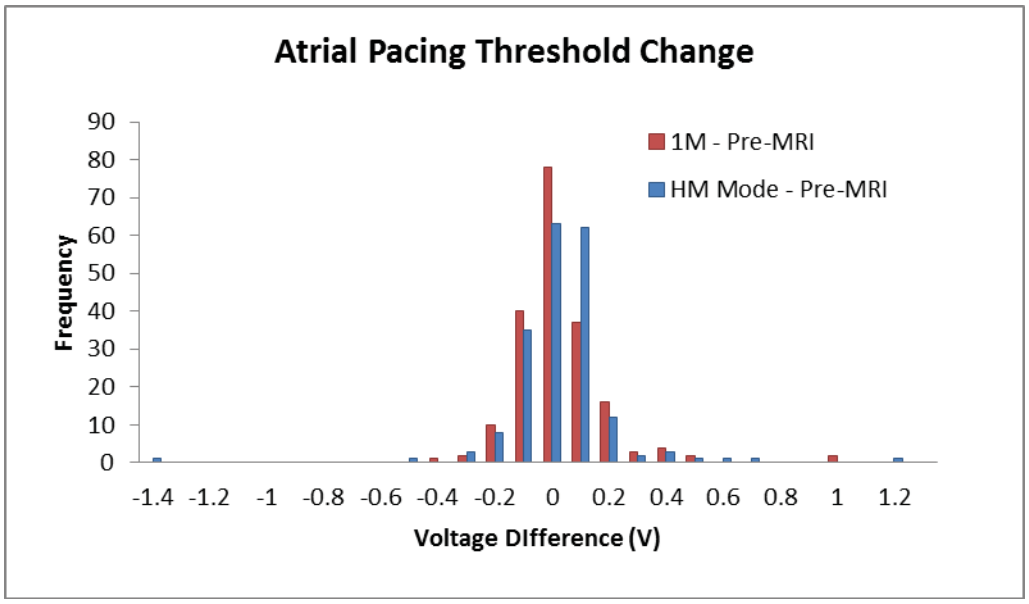
In addition, FDA asked for more detailed analyses of the Home Monitoring data in the interactive clinical questions.

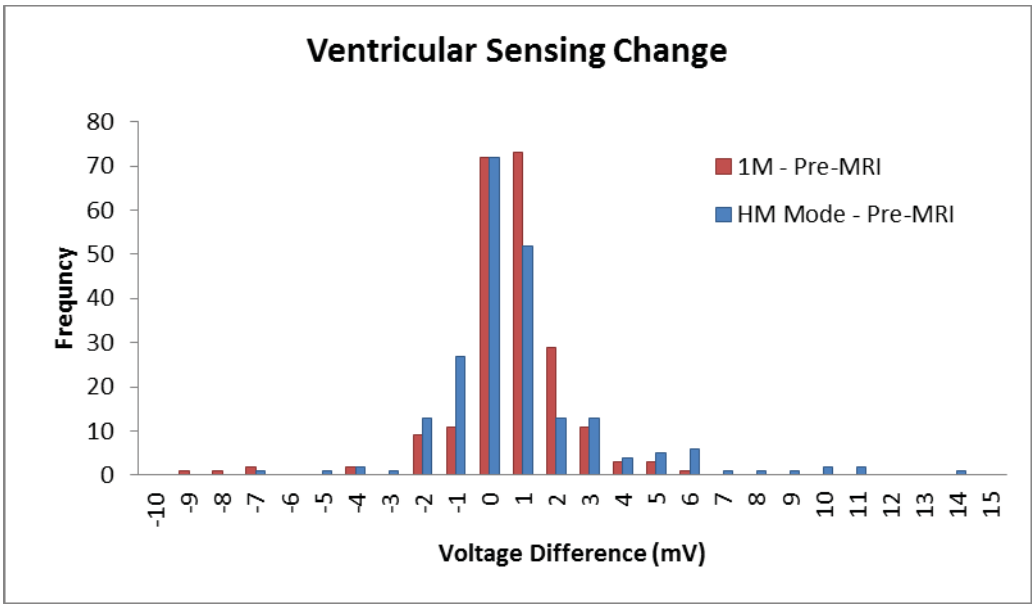
> **Question #5**: In Section 2.6.8 Home Monitoring Trending of the clinical report (page 1862 of the submission), you provided an average of the trend data obtained during the study. While this presentation is helpful, FDA is unable to evaluate the changes in pacing capture thresholds, sensing values, or impedance values in individual patients, either related to the MR scan or normal variations independent of the MR scan. FDA believes that more detailed analyses would help to demonstrate the performance of your pacemaker system following MR scans. Please provide an analysis and presentation of individual patient data along with a comparison of how the data provided through Home Monitoring compared to data collected during in office visits.

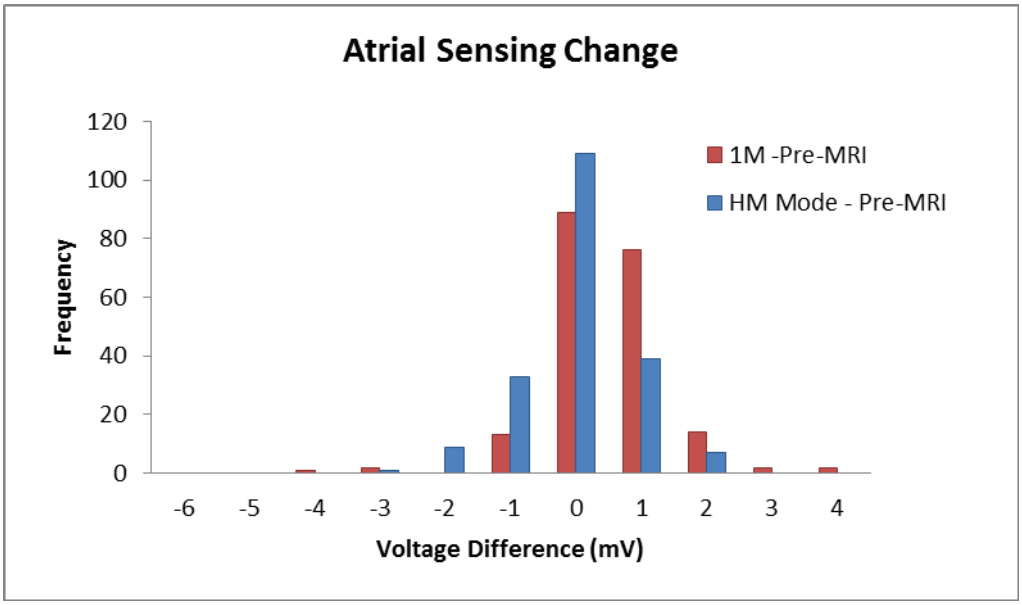
The firm provided the following additional analyses as part of the interactive response (part 1 of 2, March 7, 2014).

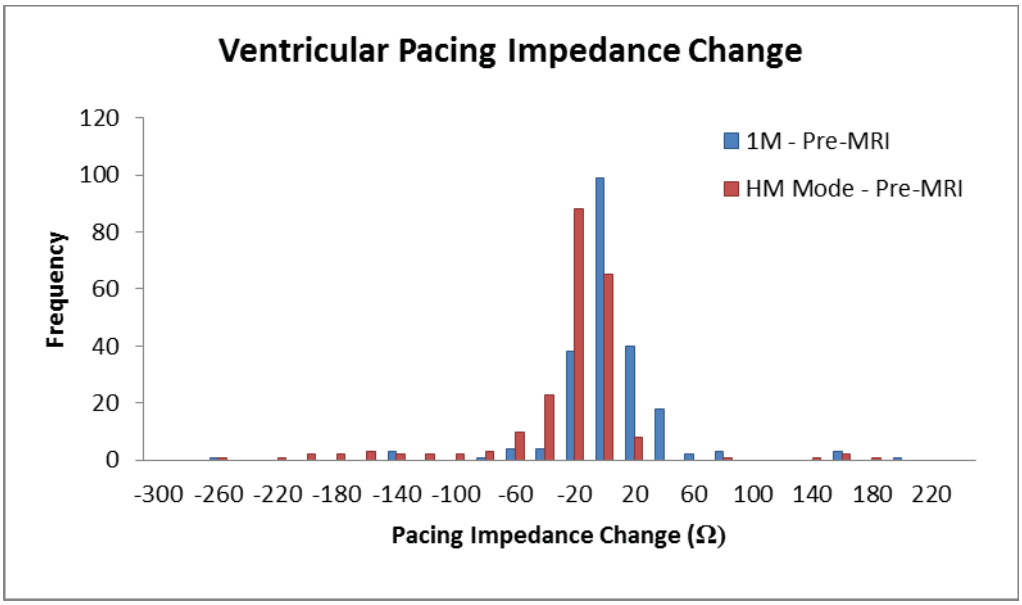
The following six charts are histograms of per-patient pacing threshold data, sensing amplitude data and lead impedance data. Each plot contains a histogram of the difference between the 1-month (1M) office visit data and the Pre-MRI data (blue bars), as well as a histogram of the difference between the mode of the Home Monitoring data (HM Mode) and the Pre-MRI data (red bars). The mode is the most commonly occurring value during the 30-days between the MR scan and the 1-month follow-up, based on daily lead measurements (~30 measurements per patient). Using the mode eliminates the variability made in any one lead measurement, at a given 1-month follow-up.

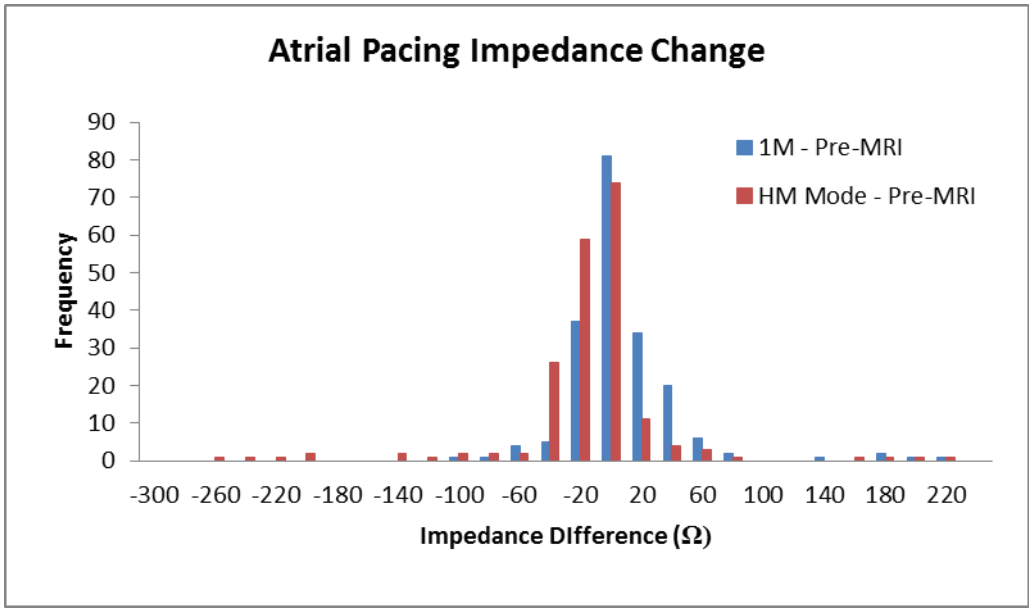

Ventricular Pacing Threshold Change
Frequency
100
90
80
70
60
50
40
30
20
10
0
-0.8 -0.6 -0.4 -0.2 0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6
Voltage Difference (V)
1M - Pre-MRI
HM Mode - Pre-MRI


Atrial Pacing Threshold Change
Frequency
90
80
70
60
50
40
30
20
10
0
-1.4 -1.2 -1 -0.8 -0.6 -0.4 -0.2 0 0.2 0.4 0.6 0.8 1 1.2
Voltage DIfference (V)
1M - Pre-MRI
HM Mode - Pre-MRI


Ventricular Sensing Change
Frequncy
80
70
60
50
40
30
20
10
0
-10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Voltage Difference (mV)
1M - Pre-MRI
HM Mode - Pre-MRI


Atrial Sensing Change
Frequency
120
100
80
60
40
20
0
-6 -5 -4 -3 -2 -1 0 1 2 3 4
Voltage Difference (mV)
1M -Pre-MRI
HM Mode - Pre-MRI





The similarities in the histograms of per-patient pacing threshold, sensing amplitude or lead impedance changes post MRI, demonstrate that these changes in individual patients are likely normal variations independent of the MR scan. Furthermore, the Home Monitoring data is consistent with the in-office threshold measurements demonstrating that this surveillance method could be used to closely monitor patients following MR scans.

FDA believes that this additional data, beyond the data collected and presented in support of the pre-defined study endpoints, further supports a reasonable assurance of safety and effectiveness of the pacemaker system when used in an MR environment.

CONSULTANT REVIEWS (FOR THE INITIAL PMA SUPPLEMENT)

Multiple subject matter experts were consulted during the review of this file. These consultants were asked to review the relevant sections of the submission and provided written consult memos. Many of these consultants were involved in the review of the firm's previous Pre-IDE, Q-Sub, and IDE submissions. The following bullets outline the consultants included in the review team:

- Clinical and Physician Labeling Consult – Brian Lewis
- Statistical Consult – Yao Huang
- Statistical Consult – Leonardo Angelone
- Animal Testing Consult – Judy Davis
- Software Consult – Dharmesh Patel
- EMC and Wireless Coexistence Consult – Seth Seidman
- Post Approval Studies Consult – Daniel Canos

Initial Consultant Review – Clinical and Physician Labeling

Brain Lewis reviewed the relevant sections of the submission and provided a review memo. In general, I concur with the comments included in the memo. Brian did not have any major deficiencies. He stated, "The submission provides robust reassurance that clinically important adverse events did not occur when the proposed pacing system was exposed to controlled MR scanning under the specific conditions of use outlined in this submission." Brian did have some requests for additional information, which FDA previously shared with the firm during our previous interactions during the Pre-IDE and IDE discussions. We met to discuss these questions on February 12, 2014. Those comments and questions were sent to the firm as part of the interactive review process and appear below in the section titled Interactive Questions for the Sponsor (February 23, 2014).

Regarding the labeling, it is important to note that all of the information relevant to MRI scanning and conditions appears in the Entovis ProMRI System Technical Manual (Appendix 99 of the submission), not in the Entovis (pulse generator) Technical Manual.

In addition, the following text was added to the device description section of the Entovis (pulse generator) technical manual:

> "Refer to Section 16 of this manual for the Entovis ProMRI system of devices. Refer to the Entovis ProMRI Technical Manual for specific MR conditions of use."

The following text was removed from the Warnings and Precautions section of the Entovis (pulse generator) technical manual:

> "Magnetic Resonance Imaging (MRI) — Avoid use of magnetic resonance imaging as it has been shown to cause movement of the pulse generator within the subcutaneous pocket and may cause pain and injury to the patient and damage to the pulse generator. If the procedure must be used, constant monitoring is recommended, including monitoring the peripheral pulse."

There is also relevant information on the Entovis ProMRI System Patient ID Cards (Appendix 100 of the submission). The bottom of the patient identification card states, “This system is approved for MRI when used according to system labeling”.

Initial Consultant Review – Statistical

Yao Huang reviewed the relevant sections of the submission and provided a review memo. In general, I concur with the comments included in the memo. Yao did have questions about the statistical analyses. We met to discuss these questions on February 12, 2014. Those comments and questions were sent to the firm as part of the interactive review process and appear below in the section titled Interactive Questions for the Sponsor (February 23, 2014).

Initial Consultant Review – MR-Related Heating

Leonardo Angelone reviewed the relevant sections of the submission and provided a review memo. Wolfgang Kainz supported Leonardo in his review of the file, based on his previous reviews and interactions with the firm during Pre-IDE, IDE, and Q-Sub process. In general, I concur with the comments included in the memo. As part of the face-to-face discussion with the firm on February 4, 2014 (as part of Q131607), we discussed the MR heating results and resolved the previous future considerations from the supporting study, G120226. Based on their review and the discussion at the meeting, Leonardo and Wolfgang did not have any remaining deficiencies.

Initial Consultant Review – Animal Testing

Judy Davis reviewed the relevant sections of the submission and provided a review memo. In general, I concur with the comments included in the memo. As part of the face-to-face discussion with the firm on February 4, 2014 (as part of Q131607), we discussed the tissue pathology results and resolved the previous future considerations from the supporting study, G120226. Based on her review and the meeting, Judy did not have any remaining concerns.

Initial Consultant Review – Software

Dharmesh Patel reviewed the relevant sections of the submission and provided a review memo. In general, I concur with the comments included in the memo. Dharmesh did not have any remaining concerns.

Initial Consultant Review – EMC and Wireless Coexistence

Seth Seidman reviewed the relevant sections of the submission and provided a review memo. In general, I concur with the comments included in the memo. Seth did have questions about the EMC testing. Those comments and questions were sent to the firm as part of the interactive review process and appear below in the section titled Interactive Questions for the Sponsor (February 23, 2014).

Initial Consultant Review – Post Approval Studies

Daniel Canos reviewed the relevant sections of the submission and provided a review memo. In general, I concur with the comments included in the memo. The firm provided additional information as rationale for not conducting a post approval study. Further discussion will need to occur with the review team and the sponsor before a recommendation is made on the post approval study requirements. Additional discussions were held regarding this topic and are summarized in the Post Approval Study Discussions section below.

Q131607 INTERACTIVE MEETING

During the review of I100712 and G120226, FDA shared our questions and concerns with the sponsor, during informal discussions, formal meetings, and official letters (as deficiencies and future concerns). As a result, the firm was aware of our questions and was actively working to address those issues, even prior to submission of the PMA Supplement. The firm submitted Q131607 during FDA's review of the PMA Supplement, to address the questions raised during FDA's review of the IDE clinical study.

On January 29, 2014, as part of Q131607, we conducted an internal meeting to discuss the information that the firm provided to address previous future considerations for Q120226/S010. Those future considerations also applied to the firm's original IDE submission and therefore applied to this PMA Supplement. Based on our discussion, we agreed that it would be best to focus our face-to-face discussion on power dissipation and temperature changes of the lead tip.

On February 4, 2014, we met face-to-face with the firm to discuss Q131607, with a focus on power and heat dissipation at the lead tip. The firm provided a presentation, which included an excellent outline of the timeline of the submissions, their testing plans, and a comparison of their data to data from other firms. The firm provided draft meeting minutes, which were reviewed and revised by FDA. The meeting minutes and presentation were provided. Following the meeting, the firm also provided some additional information about energy levels.

INTERACTIVE QUESTIONS FOR THE SPONSOR (FEBRUARY 23, 2014)

Based on FDA's review of data and analyses provided in the PMA Supplement, as well as the subsequent clarifying discussions during the review of Q131607, the review team did not have any major deficiency questions. However, the team did have clinical, statistical, and EMC questions that could be handled interactively with the firm. Deficiency questions were developed and refined based on recommendations from and discussions with the supporting consultants. The decision was made to "proceed interactively", and the questions were sent to the sponsor on February 23, 2014, following branch-level and division-level review and concurrence. FDA then had an interactive discussion with the sponsor on February 28, 2014.

Introductory Text

FDA has completed our initial review of your submission. Based on our review of the submission and your request, we would like to proceed interactively. After you review the following questions, FDA would like to schedule a teleconference call with you to discuss any clarification that you might need regarding these questions. In order to meet our mutual goals, you will need to quickly answer these and any other questions provided by FDA, including questions about labeling and possible post approval study requirements. We look forward to interactively working with you to complete our review.

General Interactive Questions

1. As discussed with you interactively on February 13, 2014, FDA believes that your per-protocol analyses should include at least the minimum number of subjects identified in the sample size requirements for your clinical protocol. Specifically, your clinical protocol required 154 evaluable subjects with an atrial lead, but your clinical report includes only data from only 136 subjects. Please update all of your descriptive and statistical analyses for your clinical report to include a more recent set of subjects with data for each of the endpoints. Your updated report should fulfill the minimum

sample size for all of the primary endpoints. The following sections include questions that you may consider answering interactively with FDA while you update your report to include the revised data set and supporting analyses. Please note that you will also need to update your proposed clinical summary in your labeling.

Clinical Interactive Questions

2. In Section 2.6.7 Multiple MRI Scans of the clinical report (page 1861 of the submission), you stated that there were 4 US subjects that had multiple MR scans: one clinically indicated scan and one non-indicated scan. FDA believes that the data from patients with multiple scans may be supportive of your overall submission. Please provide the changes in pacing capture thresholds, sensing values, and impedance values for these subjects.

3. The clinical report shows that approximately half of systems had been implanted for 30-60 days at the time of enrollment, 16% between 60-90 days at the time of enrollment, and 24% between 90-180 days at the time of enrollment. A few systems, 6.4%, were implanted greater than 6 months. FDA believes that there might be differences in the changes in the pacing capture threshold and sensing values, depending on the implant duration. Please provide analyses of this information and a rationale for any identified differences.

4. Your submission included your proposed labeling, which included instructions for performing MR scans (a checklist and quick reference guide on page 1937 of the submission). However, it is unclear how physicians would locate the most relevant information on your website, given that the appropriate printed information might not be available months or years after the device is implanted. Therefore, FDA believes that the most relevant information should also be easy to find and access on your website. Please provide an explanation of how physicians would locate this information on your web site.

5. In Section 2.6.8 Home Monitoring Trending of the clinical report (page 1862 of the submission), you provided an average of the trend data obtained during the study. While this presentation is helpful, FDA is unable to evaluate the changes in pacing capture thresholds, sensing values, or impedance values in individual patients, either related to the MR scan or normal variations independent of the MR scan. FDA believes that more detailed analyses would help to demonstrate the performance of your pacemaker system following MR scans. Please provide an analysis and presentation of individual patient data along with a comparison of how the data provided through Home Monitoring compared to data collected during in office visits.

6. During your Pre-IDE discussions with us, we requested that you evaluate how cardiology and radiology teams worked together in order to safely and easily perform MR scans. FDA was unable to locate a discussion about your experiences, which might include lessons learned or modifications to the instructions for use that resulted from your experiences. Please identify where to find this information in your submission or provide this information.

7. Your clinical report included a summary of serious (Table 13) and non-serious (Table 14) adverse events. The reported adverse events included some instances of arrhythmias. FDA previously expressed a concern about the potential for induction of arrhythmias as a result of the MR scan. Please explain how these adverse events might be related or unrelated to the MR scanning procedure.

8. In Section 2.4.4 Implanted Devices of the clinical report (page 1848 of the submission), you provided a summary of the implanted pulse generators used during the study. FDA noted that approximately

11% of the devices were single-chamber systems. FDA believes that the effects of MR scans might differ between single and dual-chamber pacemaker systems. Please compare the changes in pacing capture threshold, sensing values, and impedance values between these two types of systems and demonstrate the poolability of the results. As part of your comparison, please provide and evaluate the data for individual systems, rather than averaging the data from each group.

Statistical Interactive Questions

9. FDA noted that the safety evaluation was conducted based on 184 subjects that completed the one-month follow-up visit plus 2 subjects that either missed the one-month visit or exited the study (Figure 1, Pages 1846 of 8720 and 1849 of 8720). However, according to Figure 1, a total of 202 subjects went through the intended MRI procedure. FDA requests that you consider including all of the treated 202 subjects in the safety assessment. Please conduct a sensitivity analysis based on all treated subjects to evaluate device safety.

10. According to the protocol for the ProMRI Study (G120226), the intent-to-treat (ITT) population should consist of all enrolled subjects. However, it appeared that inconsistent definitions for the ITT population were used for different endpoint (Table 8, Page 1849 of 8720). Please clarify the discrepancies in the ITT analyses.

11. For Primary Endpoint #2, you stated that a pre-specified intent-to-treat (ITT) analysis was conducted using imputed Home Monitoring values and resulted in a PPT = 99.4% (162/163) (Page 1851 of 8720). FDA believes that the ITT population should include all subjects that were enrolled, regardless of whether or not data was available for the endpoints. Therefore, FDA believes that the analysis that you provided is truly an ITT analysis. FDA's concern also applies to Primary Endpoints #3 (Page 1853 of 8720), #4 (Page 1855 of 8720), and #5 (Page 1856 of 8720), respectively. Please address this issue for each of the endpoints.

12. For Primary Endpoint #2, an "additional intent-to-treat analysis" was also conducted with two missing values classified as failure due to a lack of Home Monitoring data and resulted in PPT = 98.2% (162/165) with p=0.033 and 95% confidence interval of (94.8%, 99.6%) (Page 1851 of 8720). FDA believes that this analysis should be considered as the intent-to-treat analysis because this analysis includes all enrolled subjects. FDA noted that the 95% lower confidence bound was 94.8%, which is less than the pre-specified performance goal of 95%. Please discuss and address this concern.

13. In Section 3 Discussion and Conclusion of the clinical report (page 1867 of the submission), your summary refers only to the per-protocol analyses. According to the clinical protocol, the endpoints should also be analyzed and presented using the intent-to-treat population. Please update the summary to include both analyses.

14. In Table 1: Clinical Study Design Comparison of the clinical report (page 1840 of the submission), you compare the ProMRI Study (G120226) and the ProMRI AFFIRM Study (I100712). In the table, you indicated that both studies would enroll 245 subjects, respectively. However, FDA's examination of the protocols for G120226 and I100712 indicates that the sample size for G120226 would be 245 subjects and the sample size for I100712 would be 299 subjects. Please clarify this discrepancy.

15. In Table 1: Clinical Study Design Comparison of the clinical report (page 1840 of the submission), there is no information about the statistical analysis plan for each study. FDA's examination of the protocols for the two studies identifies an important difference. The ProMRI Study (G120226) states that Primary Endpoints #4 and #5 would be evaluated against pre-specified performance goals, while the ProMRI AFFIRM Study (I100712) endpoints would be evaluated through a non-inferiority test.

FDA would like clarification about the rationale for these differences and their potential impact on poolability of the data. Please discuss and address these concerns.

16. In Table 2: Distribution of Enrollment of the clinical report (page 1843 of the submission), you indicated that 133 subjects were enrolled in the ProMRI Study (G120226) and 122 subjects were enrolled in the ProMRI AFFIRM Study (I100712). Therefore, your submission includes a total of 255 subjects. However, the study protocols required a sample size of 245 subjects for the ProMRI Study and a sample size of 299 subjects for the ProMRI AFFIRM study. Therefore, neither study was successfully completed nor included the minimum number of enrolled subjects. Please explain your rationale for not fulfilling the prespecified requirements included in each protocol and your rationale for why pooling of the data is appropriate in support of your submission. In addition, FDA identified a number of discrepancies. For example, the introductory text for this table refers to "219 enrolled subjects". As another example, you stated that a total of 17 sites had an enrollment less than or equal to the median of 3 subjects, with 14 sites having an enrollment of greater than 3 subjects (Page 1872 of 8720). However, Table 2 (Page 1843 of 8720) indicated that only 11 sites had enrollment less than or equal to 3 subjects while 24 sites had enrollment more than 3 subjects. Please clarify these discrepancies.

17. You indicated that a poolability analysis across sites was conducted with a p-value of 0.559 (page 1872 of the submission). You also stated that the analysis was based on data from 31 sites. According to Table 2 on page 1843 of the submission, there were 35 participating sites from the two studies. Please clarify why the poolability was conducted based on 31 of the 35 sites and which sites were excluded from the analysis. Please also provide details on how the poolability analysis was conducted.

EMC Testing Interactive Questions

18. You submitted testing per ISO 14117 on your device. ISO 14117 does not fully cover exposure to RFID readers, which have been documented to interfere with implantable pacemakers. While FDA understands that you are not requesting to modify the hardware of your device, the electromagnetic environment is always changing and the continuing emergence of RFID is well known as an emitter in that environment. Please demonstrate that your device is safe and effective with regard to exposure from RFID systems.

INTERACTIVE RESPONSES FROM THE SPONSOR (PART 1 OF 2, MARCH 7, 2014)

The firm provided the part 1 of 2 of the interactive response. The submission included responses to interactive questions 2, 3, 5, 8, and 14-18.

Brian Lewis provided his review of the firm's initial responses. From his perspective, the firm's responses are sufficient to address his concerns. He asked for clarification about the data presented for interactive clinical question #5. I forwarded his question to the firm on March 20, 2014. The firm confirmed that the data was analyzed in the way that Brian Lewis' had assumed.

Yao Huang provided her review of the firm's initial responses. From her perspective, the firm's responses are sufficient to address her concerns.

I reviewed the firm's response to Question #18 regarding radio frequency identification (RFID) readers. The firm explained that, in addition to the testing per the EMC protocols required by ISO 14117:2012 and

ANSI/AAMI PC69:2007, they conducted radiated electromagnetic emissions tests in the frequency range of 219 Hz to 2MHz with continuous wave, pulsed modulated, and frequency modulated signals to test the device immunity to Electronic Article Surveillance equipment. The device was subjected to frequencies, modulations, and field strengths determined from published reports with respect to Electronic Article Surveillance equipment. The testing demonstrates that the device is immune to the radiated emissions from these types of fields and energies. The testing is documented in (b)(4) TS/CCI which was provided in Appendix 74 of PMA Supplement P950037/S132. The firm also submitted their validation test design (b)(4) TS/CCI for electronic article surveillance testing as an appendix. As a reminder, the firm is not modifying their device. Rather, this PMA Supplement is requesting approval for MR conditional labeling, and I believe that the firm has conducted and submitted the appropriate bench testing for this request. The firm also stated that they have sold (b)(4) TS/CCI these devices worldwide and that they have not received any complaints related to interactions with RFID or other similar systems. Based on my review of the firm's response, FDA does not have any remaining concerns regarding this issue.

INTERACTIVE RESPONSES FROM THE SPONSOR (PART 2 OF 2, MARCH 20, 2014)

The firm provided their interactive responses to the remaining questions, using the updated clinical data set, as well as updated labeling. I sent a consult request to Brian Lewis and Yao Huang, requesting a final review of the firm's updated clinical report and analyses, including responses to the remaining interactive responses.

Brian Lewis provided his review of the firm's responses, using the updated clinical data set. The firm's response addressed his remaining questions.

Yao Huang provided her review of the firm's responses, using the updated clinical data set. The firm's response addressed her remaining questions.

POST APPROVAL STUDY DISCUSSIONS

The initial PMA Supplement submission did not include a section discussing possible Post Approval Study requirements. I contacted the firm to request additional information about their plans for a post approval study, because the submission did not include a proposal. Based on my request, the firm provided some additional information about their rationale for not conducting a post approval study. I contacted Daniel Canos to review the potential Post Approval Study requirements. I forwarded the additional information provided by the firm to Daniel. As background, Daniel Canos provided some background information about the post approval study requirements for a previously approved MR-conditional pacemaker system. In contrast to the device from Medtronic, Biotronik used pulse generators and leads that were already reviewed and approved by FDA, rather than new/modified versions of devices.

I coordinated an internal meeting to review the possible need to collect Post Approval Study data, especially to address questions about multiple scans. Daniel Canos, Veronica Sansing, Brian Lewis, and I participated in the discussion. Following our internal discussion, we conducted a teleconference with the firm. Following the discussion, the firm provided meeting minutes and additional information about multiple MR scans. In addition, the firm also included some information about multiple scan in their interactive response (part 1 of 2, March 7, 2014).

As a result of the discussion with the firm about the post approval study, FDA reviewed the scanning sequences from the pre-market study that Medtronic used to support their PMA. Both the Biotronik pre-market study and the Medtronic pre-market study include two scans: one scan of the head and one scan of the spine. Sunder Rajan provided the background about the rationale for these two scans.

As a result of our interactions with the firm, there was a discussion about comparing power levels and anticipated changes in pacing thresholds that might be associated with various power levels. There may be differences in the results (e.g. differences in pacing threshold changes) that are related to confounding variables such as the length of MR exposure and the timing of the pacing capture threshold measurement.

All of this information was shared with the Post Approval Study review team, and the team agreed that requiring a study solely to evaluate the effects of multiple scans would not be appropriate for a number of reasons. First, the firm is already planning to re-enroll and re-scan patients enrolled and scanned in the first trial (phase A) into a second trial (phase B, full body scan, with no exclusion zone). As a result, they will gather and submit additional information about multiple scans to FDA as they continue to enroll and complete this study. Second, the firm collected information about changes in pacing capture thresholds, measured with increments of 0.1 Volts, as compared to 0.5 Volts in the previous study for Medtronic pulse generators. Third, the firm captured, at FDA's request during the study planning process, additional information about changes in pacing capture thresholds using their Home Monitoring system. This information demonstrates the natural variations in pacing capture thresholds and the absence of significant effects from MR scanning. Fourth, based on various internal discussions about MR scans and power levels, the duration of scan and interval between scans also affects the heating of the lead tip and any impact on pacing capture thresholds. These factors would not be well controlled in a practical setting, outside of the clinical study, and therefore the value of data gathered from a post approval study would be very limited. Therefore, FDA believes that the standard post market controls and reporting requirements for pacemaker systems in general will be sufficient to evaluate the long term experience with MR scanning as well as the safety of multiple scans.

INTERACTIONS WITH SPONSOR AND OTHER FDA STAFF (CHRONOLOGICALLY ORDERED)

The primary contact for the sponsor is Jon Brumbaugh (503-451-8310, Jon.Brumbaugh@biotronik.com).

December 16, 2013

I identified the appropriate members of the review team and assigned consults to each person.

I contacted the firm to request additional information about their plans for a post approval study, because the submission did not include a proposal.

January 2, 2014

Based on my request, the firm provided some additional information about their rationale for not conducting a post approval study.

January 29, 2014

As part of Q131607, we conducted an internal meeting to discuss the information that the firm provided to address previous future considerations for (b)(4) TS)(4) TS/CCI Those future considerations also applied to

the firm's original IDE submission and therefore applied to this PMA Supplement. Based on our discussion, we agreed that it would be best to focus our face-to-face discussion on power dissipation and temperature changes of the lead tip.

February 4, 2014

We met face-to-face with the firm to discuss Q131607, with a focus on power and heat dissipation at the lead tip. The firm provided a presentation, which included an excellent outline of the timeline of the submissions, their testing plans, and a comparison of their data to data from other firms. The firm provided draft meeting minutes, which were reviewed and revised by FDA. The meeting minutes and presentation were provided. Following the meeting, the firm also provided some additional information about energy levels.

February 12, 2014

I met with Brian Lewis and Yao Huang to discuss their review memos and questions. Based on the discussion, I contacted the firm to request clarification about their decision to submit and the resulting sample sizes.

February 13-14, 2014

The firm provided some additional information explaining their rationale for the report cutoff and resulting sample sizes. Based on the information provided by the firm, I believe that the clinical and statistical questions are not major deficiencies but can be addressed interactively with the firm.

February 18, 2014

I prepared a draft email with interactive questions for the firm. The email will be sent when the file receives branch and division concurrence.

February 23, 2014

I sent interactive questions were sent to the firm.

February 28, 2014

We reviewed the interactive questions with the firm during a teleconference, in order to provide any clarifications that would help them to address our concerns. In addition, we suggested that the firm update the clinical report with additional data and clarified which questions should be addressed now, as opposed to which questions should be addressed with the updated clinical data set.

March 5, 2014

I contacted Daniel Canos to review the potential Post Approval Study requirements. I also forwarded some additional information provided by the firm, which included a rationale for not conducting a Post Approval Study.

March 7, 2014

The firm provided the part 1 of 2 of the interactive response. The submission included responses to interactive questions 2, 3, 5, 8, and 14-18.

March 11, 2014

Daniel Canos provided some background information about the post approval study requirements for a previously approved MR-conditional pacemaker system.

March 12, 2014

Brian Lewis provided his review of the firm's initial responses. From his perspective, the firm's responses are sufficient to address his concerns. He asked for clarification about the data presented for interactive clinical question #5. I forwarded his question to the firm on March 20, 2014.

March 18, 2014

Yao Huang provided her review of the firm's initial responses. From her perspective, the firm's responses are sufficient to address her concerns.

March 20, 2014

The firm provided their interactive responses to the remaining questions, using the updated clinical data set, as well as updated labeling.

I contacted the firm to obtain clarification about their response to interactive clinical question #5.

March 21, 2014

In response to Brian Lewis' question about the histogram data for interactive clinical question #5, I sent an email to the firm asking them to confirm their analysis method. The firm confirmed that the data was analyzed in the way that Brian Lewis' had assumed.

I coordinated an internal meeting to review the possible need to collect Post Approval Study data, especially to address questions about multiple scans. Daniel Canos, Veronica Sansing, Brian Lewis, and I participated in the discussion. Following our internal discussion, we conducted a teleconference with the firm. Following the discussion, the firm provided meeting minutes and additional information about multiple MR scans.

March 25, 2014

I sent a consult request to Brian Lewis and Yao Huang, requesting a final review of the firm's updated clinical report and analyses, including responses to the remaining interactive responses.

March 31, 2014

As a result of the discussion with the firm about the post approval study, FDA reviewed the scanning sequences from the pre-market study that Medtronic used to support their PMA. Both the Biotronik pre-market study and the Medtronic pre-market study include two scans: one scan of the head and one scan of the spine. Sunder Rajan provided the background about the rationale for these two scans.

April 3, 2014

As a result of our interactions with the firm, there was a discussion about comparing power levels and anticipated changes in pacing thresholds that might be associated with various power levels. There may be differences in the results (e.g. differences in pacing threshold changes) that are related to confounding variables such as the length of MR exposure and the timing of the pacing capture threshold measurement.

April 9, 2014

Brian Lewis provided his review of the firm's responses, using the updated clinical data set. The firm's response addressed his remaining questions.

April 10, 2014

Yao Huang provided her review of the firm's responses, using the updated clinical data set. The firm's response addressed her remaining questions.

April 11, 2014

At my request, the firm provided an updated summary of the various lab and bench studies supporting their MR-conditional labeling, based on the additional analyses and interactions between the firm and FDA that occurred as a result of Q131607.

April 30, 2014

The firm contacted me to clarify the market names of the leads that would appear in the approval order.

May 1, 2014

I contacted the firm to obtain clarification about the presentation of the Home Monitoring lead measurement data presented in the initial PMA Supplement as well as the firm's interactive response (part 1 of 2).

May 2, 2014

During branch-level and division-level review of the review memo and official letter, questions were raised about the labeling being proposed by the sponsor. More specifically, concerns were raised about the lack of MR-conditional text in the Entovis pulse generator technical manual and the Selox/Safio technical manual. The firm included the conditions in a separate piece of labeling, the Entovis ProMRI Pacemaker System Manual. I contacted the firm to request clarification about their method of explaining the MR conditions and instructions for use. The firm explained that their approach was to provide the most relevant information in an easy-to-access format, rather than forcing the clinician to look through the much larger Entovis pulse generator manual. It is important to note that the healthcare providers typically access the manual online, because the printed technical manuals have not been included with the product for some time. The firm also explained the two changes in the Entovis pulse generator technical manual: 1) adding a reference to a separate manual for the MR conditions, and 2) removing the blanket warning about use of the pulse generator in an MR environment. The technical manual for the pacemaker leads was not being modified because that manual did not include any references to MR. This approach was discussed with division management and also with PMA staff. FDA staff agreed that the method of labeling being proposed by the firm appears to be appropriate, especially considering that the pulse generator and pacemaker leads have already been reviewed and approved by FDA.

May 4, 2014

Modifications were proposed to the draft approval letter, in order to address the remaining concerns about how the Setrox/Safio leads were being referenced, especially because the firm was not making modifications to the technical manual for the leads. The following text was proposed:

"…which requested approval for MRI-conditional labeling for the Entovis SR / SR T / DR / DR-T pacemakers, and the supporting Programmer Software Version PSW 1307.U. When an Entovis Pacemaker is used in conjunction with Setrox S 53/60 or Safio 53/60 pacemaker leads it shall be identified as the Entovis ProMRI System."

I believe that the modified text is accurate and more appropriately identifies the components of the system in a clear and concise manner.

May 5, 2014

I received and incorporated suggestions to clarify that this 180-Day PMA Supplement is only a request for a labeling change, in order to support MR-conditional labeling for a system, that includes pacemakers and pacemaker leads that were previously reviewed and approved by FDA. These modifications to the Purpose of Submission section of the lead review memo mimic the changes made to the official approval letter.

CONCLUSION

The FDA review team completed its review of the sponsor's request to provide MR-conditional labeling for the Entovis ProMRI Pacemaker system. FDA evaluation considered the following information:

- Initial PMA Supplement submission text and appendices
- Discussions and documentation provided as part of Q131607
- Firm's response to FDA's 18 interactive questions (part 1 of 2)
- Firm's response to FDA's 18 interactive questions (part 2 of 2), updated clinical report, and updated MR-conditional labeling
- Multiple face-to-face and teleconference meetings with the firm
- Additional documents that were requested and submitted during FDA's interactive review of the PMA Supplement
- Documentation and materials submitted during FDA's review of materials submitted during the Pre-IDE, Pre-Sub, and IDE process

Based on all of this information, I believe that the firm has demonstrated a reasonable assurance of safety and effectiveness of their pacemaker system when used in an MR environment, under the specific defined conditions included in the labeling.