# SUMMARY OF SAFETY AND EFFECTIVENESS DATA

## I. GENERAL INFORMATION

Device Generic Name:
Pulse Generator (PG): Implantable Pacemaker
Lead: Steroid-eluting, endocardial, bipolar, pace/sense lead
Lead stabilizer accessory
Stylet accessories

Device Trade Name:
ImageReady™ MR Conditional Pacing System, consisting of:

The following Implantable PGs:
- INGENIO™ MRI Pacemaker, Models K175, K176 & K177
- VITALIO™ MRI Pacemaker, Models K275, K276 & K277
- FORMIO™ MRI Pacemaker, Model K279
- ESSENTIO™ MRI Pacemaker, Models L110, L111 & L131
- PROPONENT™ MRI Pacemaker, Models L210, L211 & L231
- ACCOLADE™ MRI Pacemaker, Models L310, L311 & L331

INGEVITY™ MRI Pace/Sense Lead:
- Models 7731 & 7732 (Passive-fixation, Ventricular straight)
- Models 7735 & 7736 (Passive-fixation, Preformed Atrial J)
- Models 7740, 7741 & 7742 (Active-fixation, straight)

Accessories:
- Slit Suture Sleeve Accessory, Model 6402
- ZOOM® LATITUDE™ Programing System, Model 3120
- Programmer Software Application, Model 2869 v2.02
- IS-1 Port Plug, Model 7145

Other Leads and Accessories:

INGEVITY™ Non-MRI Pace/Sense Lead:
- Models 7631 & 7632 (Passive-fixation, Ventricular straight)
- Models 7635 & 7636 (Passive-fixation, Preformed Atrial J)
- Models 7640, 7641 & 7642 (Active-fixation, straight)

Other Accessories:
- Delivery Stylet, Models 5003, 5004, 5005, 5012, 5013, 5014

Device Procode:
LWP
NVN

| | |
|---|---|
| Applicant's Name and Address: | Boston Scientific Corporation<br>4100 Hamline Avenue North<br>St. Paul, Minnesota 55112-5798 |
| Date of Panel Recommendation: | None |
| PMA Number: | P150012 |
| Date of Notice of Approval to Applicant: | April 25, 2016 |

## II. INDICATIONS FOR USE

### II. A. Ingenio and Accolade MRI Pacemaker Device Indications

The Ingenio and Accolade MRI pacemakers are indicated for the treatment of the following conditions:

- Symptomatic paroxysmal or permanent second- or third-degree AV block
- Symptomatic bilateral bundle branch block
- Symptomatic paroxysmal or transient sinus node dysfunction with or without associated AV conduction disorders (i.e., sinus bradycardia, sinus arrest, sinoatrial [SA] block)
- Bradycardia-tachycardia syndrome, to prevent symptomatic bradycardia or some forms of symptomatic tachyarrhythmias
- Neurovascular (vaso-vagal) syndromes or hypersensitive carotid sinus syndromes

Adaptive-rate pacing is indicated for patients exhibiting chronotropic incompetence and who may benefit from increased pacing rates concurrent with increases in minute ventilation and/or level of physical activity.

Dual-chamber and atrial tracking modes are also indicated for patients who may benefit from maintenance of AV synchrony.

Dual chamber modes are specifically indicated for treatment of the following:

- Conduction disorders that require restoration of AV synchrony, including varying degrees of AV block
- VVI intolerance (i.e., pacemaker syndrome) in the presence of persistent sinus rhythm
- Low cardiac output or congestive heart failure secondary to bradycardia

### II. B. INGEVITY™ Pace/Sense Lead and Accessories Intended Use/Indications

The intended use/indication information listed below is presented as written in the device labeling.

### II.C.1. Passive-fixation Non-MRI Models 7631, 7632, 7635 and 7636 and MRI Models 7731, 7732, 7735 and 7736

This Boston Scientific lead is indicated for use as follows:

- Intended for chronic pacing and sensing in the right atrium (Preformed Atrial J) or right ventricle (Straight) when used with a compatible pulse generator.

### II.C.2. Active-fixation Non-MRI Models 7640, 7641, and 7642 and MRI Models 7740, 7741, and 7742

This Boston Scientific lead is indicated for use as follows:

- Intended for chronic pacing and sensing in the right atrium and/or right ventricle when used with a compatible pulse generator.

### II.C.3. Slit Suture Sleeve Accessory Model 6402

The intended use of the slit suture sleeve accessory is:

- Use to secure and immobilize Boston Scientific INGEVITY™ leads at the venous entry site.

### II.C.4. Delivery Stylet Models 5003, 5004, 5005, 5012, 5013, and 5014

The delivery stylet accessory is indicated for us as follows:

- For use with Boston Scientific implantable transvenous leads.

## III. CONTRAINDICATIONS

### III. A. Ingenio and Accolade MRI Pacemaker Device Contraindications

These Boston Scientific pacemakers are contraindicated for patients who have a separate implanted cardioverter defibrillator (ICD) with transvenous leads.

Use of certain pacing modes and/or features available in Boston Scientific pacemakers is contraindicated for the following patients under the circumstances listed:

- Unipolar pacing or use of the MV Sensor with a Subcutaneous Implantable Cardioverter Defibrillator (S-ICD) because it may cause inappropriate therapy or inhibition of appropriate S-ICD therapy;
- Minute Ventilation in patients with both unipolar atrial and ventricular leads;

- Single-chamber atrial pacing in patients with impaired AV nodal conduction;
- Atrial tracking modes for patients with chronic refractory atrial tachyarrhythmias (atrial fibrillation or flutter), which might trigger ventricular pacing;
- Dual-chamber and single-chamber atrial pacing in patients with chronic refractory atrial tachyarrhythmias; and/or
- Asynchronous pacing in the presence (or likelihood) of competition between paced and intrinsic rhythms.

## III. B. INGEVITY™ Lead and Accessories Contraindications

### III.B.1. Passive-fixation Non-MRI Models 7631, 7632, 7635 and 7636 and MRI Models 7731, 7732, 7735 and 7736

Use of this Boston Scientific lead is contraindicated for the following patients:

- Patients with a hypersensitivity to a nominal single dose of 0.61 mg dexamethasone acetate
- Patients with mechanical tricuspid heart valves

### III.B.2. Active-fixation Non-MRI Models 7640, 7641, and 7642 and MRI Models 7740, 7741, and 7742

Use of this Boston Scientific lead is contraindicated for the following patients:

- Patients with a hypersensitivity to a nominal single dose of 0.91 mg dexamethasone acetate
- Patients with mechanical tricuspid heart valves

### III.B.3. Slit Suture Sleeve Accessory Model 6402

There are no known contraindications for the slit suture sleeve accessory.

### III.B.4. Delivery Stylet Models 5003, 5004, 5005, 5012, 5013, and 5014

There are no known contraindications for the delivery stylet accessories.

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ImageReady™ MR Conditional Pacing System labeling, INGENIO™ MRI, VITALIO™ MRI, FORMIO™ MRI, ESSENTIO™ MRI, PROPONENT™ MRI, and ACCOLADE™ MRI pacemaker labeling, and INGEVITY™ lead labeling.

## V. IMAGEREADY SYSTEM MRI CONDITIONS OF USE

Based on its use as a system versus an individual device, "Conditions of Use" apply to the ImageReady™ MR Conditional Pacing System (ImageReady System) rather than "Indications for Use." When used as a system and according to the labeled MRI Conditions of Use, the ImageReady System has been determined to meet the status of MR Conditional per ASTM F2503:2008. The MRI Conditions of Use are as follows:

The following Conditions of Use must be met in order for a patient with an ImageReady System to undergo an MRI scan. Adherence to the Conditions of Use must be verified prior to each scan to ensure that the most up-to-date information has been used to assess the patient's eligibility and readiness for an MR Conditional scan.

### Cardiology

1. Patient is implanted with the ImageReady™ MR Conditional Pacing System[4]
2. Pulse generator in MRI Protection Mode during scan
3. Bipolar pacing operation or pacing off
4. Patient does not have elevated body temperature or compromised thermoregulation at time of scan
5. Pulse generator implant location restricted to left or right pectoral region
6. At least six (6) weeks have elapsed since implantation and/or any lead revision or surgical modification of the MR Conditional Pacing System
7. No cardiac-related implanted devices, components, or accessories present other than the ImageReady™ MR Conditional Pacing System
8. Pacing threshold ≤ 2.0 V in pace-dependent patients
9. No abandoned leads or pulse generators
10. No evidence of a fractured lead or compromised pulse generator-lead system integrity

### Radiology

1. MRI magnet strength of 1.5 T only
    - Radio frequency (RF) field of approximately 64 MHz
    - Spatial gradient no greater than 50 T/m (5,000 G/cm)
2. Horizontal, $^{1}H$ proton, closed bore scanners only
3. Specific Absorption Rate (SAR) limits for Normal Operating Mode[5] or for First Level Controlled Operating Mode[6] must be observed for the entire active scan session as follows:
    - Whole body averaged, ≤ 4.0 watts/kilogram (W/Kg)
    - Head, ≤ 3.2 W/Kg
4. Gradient Field limits: Maximum specified gradient slew rate ≤ 200 T/m/s per axis

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[4] Defined as a Boston Scientific MR Conditional pulse generator and lead(s), with all ports occupied by a lead or port plug.
[5] As defined in IEC 60601-2-33, 201.3.224, 3rd Edition
[6] As defined in IEC 60601-2-33, 201.3.208, 3rd Edition

5. No local transmit-only coils or local transmit/receive coils placed directly over the pacing system; the use of receive-only coils is not restricted
6. Patient in supine or prone position only
7. The patient must be monitored during the MRI scan by pulse oximetry and/or electrocardiography (ECG)

# VI. DEVICE DESCRIPTION

## VI. A ImageReady System Description

The ImageReady™ MR Conditional Pacing System (ImageReady System) has been created specifically as a system for use with MRI scans performed under the Conditions of Use described in Section V. The Ingenio[7] MRI or Accolade MRI[8] pacemaker design has minimized use of ferromagnetic materials, which can interact with the fields generated during a typical MRI scan, and the circuits have been designed to tolerate voltages that may be induced during scans. The INGEVITY lead wire has been designed for use with the ImageReady pacemaker specifically to reduce absorption of energy from MR Fields, thus minimizing subsequent heating. The system is designed for full body scan, with no thoracic exclusion zone. The ImageReady System has mitigated risks associated with MRI scans as compared to conventional pacemakers and leads. The implanted system, as opposed to its constituent parts, is determined to have the status of MR Conditional as described in ASTM F2503:2008. Additionally, an MRI Protection Mode has been created for use during the scan. MRI Protection Mode modifies the behavior of the pacemaker and has been designed to accommodate the MRI scanner electromagnetic environment. A Time-out feature can be programmed to allow automatic exit from MRI Protection Mode after a set number of hours chosen by the user. These features have been tested to verify the effectiveness of the designs. Other MRI-related risks are further reduced by adherence to the Conditions of Use for MR Scanning specified in the Technical Guide.

## VI. B Pacemaker Device Description

The Ingenio MRI and Accolade MRI pacemakers (see **Figure 1** and **Figure 2)** are multi-programmable and consist of both dual-chamber and single-chamber models, offering adaptive-rate bradycardia therapy as well as various levels of therapeutic and diagnostic/trending functionality based upon the model.

Two sensors are available to adapt the pacing rate to the patient's changing metabolic demand. Minute Ventilation responds to change in respiration, and the accelerometer

[7] Ingenio (lower case) refers to all trademarked devices in this family of pulse generators, including ADVANTIO, INGENIO, INGENIO MRI, VITALIO, VITALIO MRI, FORMIO and, FORMIO MRI
[8] Accolade (lower case) refers to all trademarked devices in this family of pulse generators, including ESSENTIO, ESSENTIO MRI, PROPONENT, PROPONENT MRI, ACCOLADE, ACCOLADE MRI

responds to patient activity (motion). Rate adaptive models can use either the accelerometer or minute ventilation sensor, or a blend of both accelerometer and minute ventilation.


**Figure 1: Images of INGENIO ™, VITALIO™ and FORMIO™ MRI Pacemakers**


**Figure 2: Images of ACCOLADE ™, PROPONENT™ and ESSENTIO™ MRI Pacemakers**

## VI. C Lead and Lead Accessory Device Description

### VI.C.1. INGEVITY™ Pace/Sense Lead Description

The INGEVITY lead is a steroid-eluting endocardial pace/sense lead intended for implantation into the right atrium and/or right ventricle for chronic pacing and sensing.

The lead is designed to conduct intrinsic electrical signals from the cardiac tissue to a pulse generator; the IS-1 bipolar connector allows the lead to be used in conjunction with a compatible pulse generator. The six French diameter lead is offered in several lengths. The isodiametric INGEVITY lead body is a co-axial design, that includes single-filar inner and outer coils for improved flex fatigue. An open-lumen conductor coil design enables lead delivery using a stylet. The conductors are separated by both a silicone rubber and polytetrafluoroethylene (PTFE) lining. Both the inner and outer coil are covered in ethylene tetrafluoroethylene (ETFE) for extra insulation protection. The entire lead body is encompassed in a polyurethane outer insulation. The lead is equipped with a radiopaque suture sleeve that is visible under fluoroscopy and is used to secure, immobilize, and protect the lead at the venous entry site after lead placement. The lead electrodes are coated with IROX (iridium oxide) to increase the microscopic surface area.

The INGEVITY lead family includes these lead types:

- Straight, extendable/retractable fixation (active) models allow for various lead placement possibilities for the tip electrode in the right atrium and/or right ventricle;
- Straight, tined fixation (passive) models provide fixation in the apex of the right ventricle; and
- Preformed Atrial J-shaped, tined fixation (passive) models provide fixation in the atrial appendage.

Some models of the lead are MR Conditional when connected to a Boston Scientific MR Conditional pulse generator as part of the ImageReady™ MR Conditional Pacing System.

Photos of the INGEVITY Lead Family are shown in **Figure 3** and **Figure 4**.

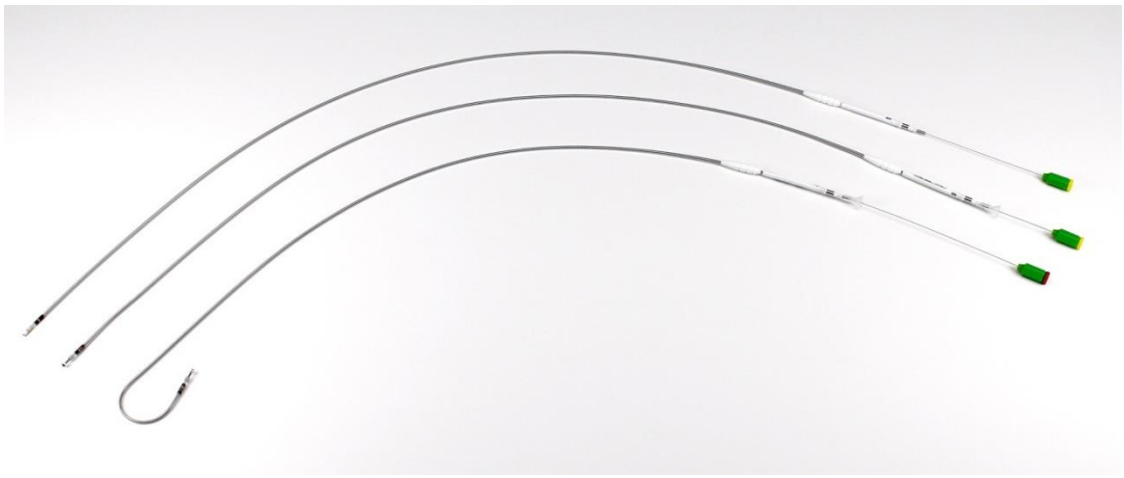

**Figure 3: INGEVITY™ Pace/Sense Lead Family**

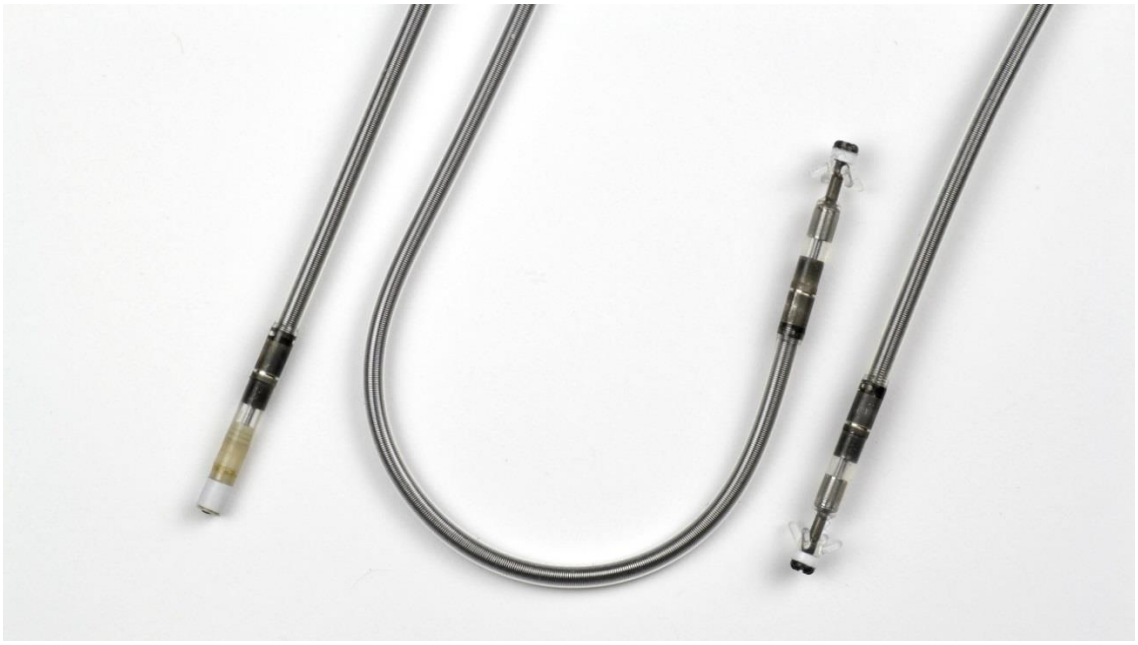

**Figure 4: INGEVITY Lead Family – Distal End Close-up**

### VI.C.2. Slit Suture Sleeve Accessory Model 6402 Description

The suture sleeve (**Figure 5**) is a radiopaque, adjustable, tubular reinforcement made of molded silicone rubber, used to secure and protect the lead at the venous entry site after placement. The silicone rubber is mixed with titanium dioxide to color it white and barium sulfate to make it radiopaque. A slit traverses the length of the suture sleeve to facilitate installation over the INGEVITY lead body.

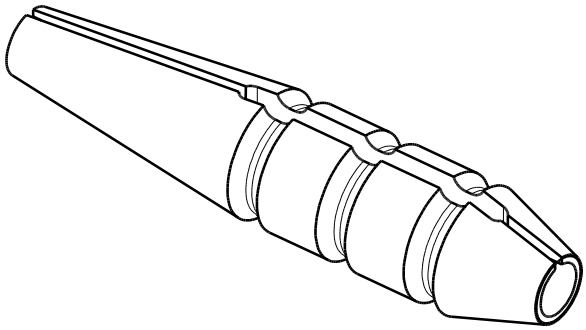

**Figure 5: Slit Suture Sleeve Model 6402**

### VI.C.3. Delivery Stylet Models 5003, 5004, 5005, 5012, 5013, and 5014

Stylet models 5003, 5004, 5005, 5012, 5013, and 5014 are separately packaged accessories intended for use with the INGEVITY™ Pace/Sense Leads. They are sterilized with ethylene oxide. The stylet cap is color-coded to visually identify the stylet length, which is also imprinted on the cap. **Table 1** provides details of each model's characteristics.

**Table 1: Stylet Descriptions**

| Stylet Model | Type | Stiffness | Length | Hub/Knob Color | Cap Color |
|---|---|---|---|---|---|
| 5003 | Straight | Extra Soft | 45 cm | Yellow | White |
| 5004 | Straight | Extra Soft | 52 cm | Yellow | Red |
| 5005 | Straight | Extra Soft | 59 cm | Yellow | Yellow |
| 5012 | Straight Long-tapered | Soft | 45 cm | Green | White |
| 5013 | Straight Long-tapered | Soft | 52 cm | Green | Red |
| 5014 | Straight Long-tapered | Soft | 59 cm | Green | Yellow |

## VII. ALTERNATIVE PRACTICES AND PROCEDURES

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

## VIII. MARKETING HISTORY

INGEVITY Leads, both non-MRI and MRI models, have received CE mark and the MRI models are approved for use with the ImageReady™ MR Conditional Pacing System. European implants began in March 2014. The INGEVITY Leads have not been withdrawn from the market in any country for any reason related to the safety and effectiveness of the system.

The non-MRI Ingenio and Accolade models are market approved in the US. Both device families are market approved internationally as well. Likewise, the Ingenio MRI and Accolade MRI models are market approved internationally. With regard to CE Mark, these Ingenio/Accolade MRI models are part of the ImageReady System with either FINELINE II Sterox and Sterox EZ leads, or with INGEVITY MRI leads. The ImageReady System has not been withdrawn from the market in any country for any reason related to the safety and effectiveness of the system. A summary of marketing status is provided in **Table 2**.

**Table 2: Market Status of ImageReady System, Ingenio and Accolade Pacemakers and INGEVITY Leads**

| Product | US Market | International Market |
|---|---|---|
| ImageReady System | FDA Approved <Date to be filled in by FDA> | CE Mark authorized for Ingenio/ Accolade MRI models with either FINELINE II Sterox and Sterox EZ leads or with INGEVITY MRI leads.<br>Also approved for Ingenio models with FINELINE II Sterox and Sterox EZ leads in Asia Pacific, Europe (non-CE Countries), Middle East/Africa and South America/Latin America. |
| Ingenio non-MRI (Lower Tier)<br>ADVANTIO<br>INGENIO | FDA Approved May 2012 | CE Mark authorized September 2011<br>Also approved in Asia Pacific, Canada, Europe (non-CE Countries), Middle East/Africa and South America/Latin America |
| Ingenio non-MRI (Upper Tier)<br>VITALIO<br>FORMIO | FDA Approved May 2013 | CE Mark authorized January 2013<br>Also approved in Asia Pacific and Canada |
| Ingenio MRI (Lower Tier)<br>ADVANTIO*<br>INGENIO | FDA Approved <Date to be filled in by FDA><br>*ADVANTIO MRI not intended for US Market | CE Mark authorized July 2012<br>Also approved in Asia Pacific, Europe (non-CE Countries), Middle East/Africa and South America/Latin America |
| Ingenio MRI (Upper Tier)<br>VITALIO<br>FORMIO | FDA Approved <Date to be filled in by FDA> | CE Mark authorized January 2013<br>Also approved in Asia Pacific, Europe (non-CE Countries), Middle East/Africa and South America/Latin America |
| Ingenio 2 (Accolade) non-MRI<br>ESSENTIO<br>PROPONENT<br>ACCOLADE | FDA Approved October 2014 | CE Mark authorized September 2014<br>Also approved in Europe (non-CE Countries) |
| Ingenio 2 (Accolade) MRI<br>ESSENTIO<br>PROPONENT<br>ACCOLADE | FDA Approved <Date to be filled in by FDA> | CE Mark authorized September 2014<br>Also approved in Europe (non-CE Countries) |
| INGEVITY non-MRI and accessories | FDA Approved <Date to be filled in by FDA> | CE Mark authorized February 2014<br>Also approved in Asia Pacific, Canada and South America/Latin America |

| Product | US Market | International Market |
|---|---|---|
| INGEVITY MRI | FDA Approved <Date to be filled in by FDA> | CE Mark authorized February 2014 and are approved for use with the ImageReady system<br>Also approved in Asia Pacific, Europe (non-CE Countries), Middle East/Africa and South America/Latin America |

## IX. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

### IX. A. ImageReady™ MR Conditional Pacing System Potential Adverse Events

Potential adverse events differ depending on whether the MRI Conditions of Use are met. For a complete list of potential adverse events, refer to the Physician's Technical Manual for the pulse generator.

MRI scanning of patients when the Conditions of Use are met could result in the following potential adverse events:

- Arrhythmia induction
- Bradycardia
- Patient death
- Patient discomfort due to slight movement or heating of the device
- Side effects of MRI Protection Mode pacing at elevated fixed rate and increased output including reduced exercise capacity, acceleration of heart failure, and competitive pacing/arrhythmia induction
- Syncope

MRI scanning of patients when the Conditions of Use are **NOT** met could result in the following potential adverse events:

- Arrhythmia induction
- Bradycardia
- Damage to the pulse generator and/or leads
- Erratic pulse generator behavior
- Inappropriate pacing, inhibition of pacing, failure to pace
- Increased rate of lead dislodgement (within six weeks of implant or revision of system)
- Irregular or intermittent capture or pacing
- Pacing threshold changes

- Patient death
- Patient discomfort due to movement or heating of the device
- Physical movement of pulse generator and/or leads
- Sensingchanges
- Syncope

### IX. B. Ingenio and Accolade Pacemaker Potential Adverse Events

- Air embolism
- Allergic reaction
- Bleeding
- Bradycardia
- Cardiac tamponade
- Chronic nerve damage
- Component failure
- Conductor coil fracture
- Death
- Elevated thresholds
- Erosion
- Excessive fibrotic tissue growth
- Extracardiac stimulation (muscle/nerve stimulation)
- Fluid accumulation
- Foreign body rejection phenomena
- Formation of hematomas or seromas
- Heart block
- Heart failure following chronic RV apical pacing
- Inability to pace
- Inappropriate pacing
- Incisional pain
- Incomplete lead connection with pulse generator
- Infection including endocarditis
- Lead dislodgment
- Lead fracture
- Lead insulation breakage or abrasion
- Lead perforation
- Lead tip deformation and/or breakage
- Local tissue reaction
- Loss of capture
- Myocardial infarction (MI)
- Myocardial necrosis
- Myocardial trauma (e.g., tissue damage, valve damage)
- Myopotential sensing
- Oversensing/undersensing

- Pacemaker-mediated tachycardia (PMT) (Applies to dual-chamber devices only)
- Pericardial rub, effusion
- Pneumothorax
- Pulse generator migration
- Shunting current during defibrillation with internal or external paddles
- Syncope
- Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation
- Thrombosis/thromboemboli
- Valve damage
- Vasovagal response
- Venous occlusion
- Venous trauma (e.g., perforation, dissection, erosion)
- Worsening heart failure

For a list of potential adverse events associated with MRI scanning, refer to the MRI Technical Guide (included above in **Section IX. A**).

Patients may develop psychological intolerance to a pulse generator system and may experience the following:

- Dependency
- Depression
- Fear of premature battery depletion
- Fear of device malfunction

### IX. C. INGEVITY™ Lead Potential Adverse Events

- Air embolism
- Allergic reaction
- Arterial damage with subsequent stenosis
- Bleeding
- Bradycardia
- Breakage/failure of the implant instruments
- Cardiac perforation
- Cardiac tamponade
- Chronic nerve damage
- Component failure
- Conductor coil fracture
- Death
- Electrolyte imbalance/dehydration
- Elevated thresholds
- Erosion

- Excessive fibrotic tissue growth
- Extracardiac stimulation (muscle/nerve stimulation)
- Fluid accumulation
- Foreign body rejection phenomena
- Formation of hematomas or seromas
- Heart block
- Hemorrhage
- Hemothorax
- Inability to pace
- Inappropriate therapy (e.g., shocks and antitachycardia pacing [ATP] where applicable, pacing)
- Incisional pain
- Incomplete lead connection with pulse generator
- Infection including endocarditis
- Lead dislodgment
- Lead fracture
- Lead insulation breakage or abrasion
- Lead tip deformation and/or breakage
- Malignancy or skin burn due to fluoroscopic radiation
- Myocardial trauma (e.g., tissue damage, valve damage)
- Myopotential sensing
- Oversensing/undersensing
- Pericardial rub, effusion
- Pneumothorax
- Pulse generator and/or lead migration
- Syncope
- Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation
- Thrombosis/thromboemboli
- Valve damage
- Vasovagal response
- Venous occlusion
- Venous trauma (e.g., perforation, dissection, erosion)

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

## X. SUMMARY OF PRECLINICAL STUDIES

Extensive pre-clinical testing was done to assess the safety and effectiveness of the ImageReady System and INGEVITY™ lead and lead accessories. Pre-clinical test methods included in vitro (bench) testing, in vivo (animal) testing, modeling, MR scanner-based testing and usability testing.

## X. A. Laboratory Studies

A series of non-clinical laboratory studies was conducted on the ImageReady™ MR Conditional Pacing System and the INGEVITY™ lead and is summarized in this section. See **Table 3** through **Table 5**.

### X.A.1. Biocompatibility Testing

**Table 3: Summary of Ingenio and Accolade Pulse Generator Biocompatibility Testing**

| Biological Effect per ISO 10993-# | Test Method | Test Result |
|---|---|---|
| ISO 10993-3: 2009 Genotoxicity | Ames Assay | Passed |
| | In vitro Mouse Lymphoma | Passed |
| | Mouse Micronucleus Assay | Passed |
| ISO 10993-3: 2009 Carcinogenicity | As the device is made of well-characterized materials and the results from the ISO 10993-3: 2009 genotoxicity studies demonstrated no mutagenic response, carcinogenicity testing was not conducted. | Not Required |
| ISO 10993-3: 2009 Reproductive Toxicity | The pulse generator does not come in direct contact with reproductive tissues, embryo or fetus. Moreover, the device has no known chemicals that have the potential to induce reproductive or developmental toxicity. | Not Required |
| ISO 10993-4: 2009 Blood interactions | Body contact is tissue/bone; therefore, Hemolysis- Direct & Indirect, Coagulation (PTT), Complement Activation, In vitro Hemocompatibility and Thrombogenicity are not required. | Not Required |
| ISO 10993-5: 2009 In vitro cytotoxicity | Cytotoxicity MEM Elution | Passed |
| ISO 10993-6: 2009 Local Implantation Effects | Combined with Chronic Toxicity per ISO 10993-11: 2009 | Passed |
| ISO 10993-10: 2010 Irritation and delayed-type hypersensitivity | Intracutaneous reactivity | Passed |
| | Guinea pig maximization Sensitization | Passed |
| ISO 10993-11: 2009 | Acute Systemic Toxicity | Passed |
| | Materials Mediated Rabbit Pyrogen Assay | Passed |

| Biological Effect per ISO 10993-# | Test Method | Test Result |
|---|---|---|
| Systemic Toxicity | Sub Acute Toxicity<br>14 Days Intravenous injection in mice | Passed |
| | Sub Acute Toxicity<br>14 Days Intraperitoneal injection in mice | Passed |
| | Chronic Systemic Toxicity combined with Local Implantation Effects per ISO 10993-6: 2009 | Passed |
| ISO 10993-13: 2004<br>Degradation of polymeric materials | Conducted for the thermoplastic polyurethane core material and the epoxy overmold material in the header.<br>No evidence of hydrolytic degradation for either material.<br>For both materials, limited oxidative degradation was noted that would not be representative of the enrivornment that the pulse generator would be exposed to in the body. | Passed |
| ISO 10993-14: 2004<br>Degradation of ceramic materials | Not applicable because there are no patient-contacting ceramic materials used on the pulse generator. | Not Required |
| ISO 10993-15: 2000<br>Degradation of metals/alloys | The only patient-contacting metal/alloy material is titanium, which is known to form a chemically stable oxide layer acceptable for the implant environment. | Not Applicable |
| ISO 10993-18: 2005<br>Chemical characterization | Profile of extractables/leachable chemicals for the thermoplastic polyurethane core material and the epoxy overmold material in the header was conducted. The extractables found are non-hazardous and present at toxicologically insignificant amounts to pose any concern to patient health. | Successfully Completed |

**Table 4: Summary of INGEVITY Lead and Slit Suture Sleeve Biocompatibility Testing**

| Biological Effect per ISO 10993-# | Test Method | Test Result |
|---|---|---|
| ISO 10993-3: 2009<br>Genotoxicity | Ames Assay | Passed |
| | In vitro Mouse Lymphoma | Passed |
| | Mouse Micronucleus Assay | Passed |
| ISO 10993-3: 2009<br>Carcinogenicity | As the lead is made of well-characterized materials and the results from the ISO 10993-3: 2009 genotoxicity studies demonstrated no mutagenic response, carcinogenicity testing was not conducted. | Not Required |

| Biological Effect per ISO 10993-# | Test Method | Test Result |
|---|---|---|
| ISO 10993-3: 2009<br>Reproductive Toxicity | The lead does not come in direct contact with reproductive tissues, embryo or fetus. Moreover, the device has no known chemicals that have the potential to induce reproductive or developmental toxicity. | Not Required |
| ISO 10993-4: 2009<br>Blood interactions | Hemolysis- Direct & Indirect | Passed |
| | Coagulation (PTT) | Passed |
| | Complement Activation | Passed |
| | In vitro Hemocompatibility | Passed |
| | Thrombogenicity | Passed |
| ISO 10993-5: 2009<br>In vitro cytotoxicity | Cytotoxicity MEM Elution | Passed |
| ISO 10993-6: 2009<br>Local Implantation Effects | Combined with Chronic Toxicity per ISO 10993-11: 2009 | Passed |
| ISO 10993-10: 2009<br>Irritation and delayed-type hypersensitivity | Intracutaneous reactivity | Passed |
| | Guinea pig maximization Sensitization | Passed |
| ISO 10993-11: 2009<br>Systemic Toxicity | Acute Systemic Toxicity | Passed |
| | Rabbit Pyrogen Assay | Passed |
| | Sub Acute Toxicity<br>14 Days Intravenous injection | Passed |
| | Sub Acute Toxicity<br>14 Days Intraperitoneal injection | Passed |
| | Chronic Systemic Toxicity | Passed |
| ISO 10993-13: 2004<br>Degradation of polymeric materials | No evidence of oxidative or hydrolytic degradation of the polyurethane material used on the lead | Passed |
| ISO 10993-14: 2004<br>Degradation of ceramic materials | The IROX ceramic material has a history of safe clinical use. Per Annex A, section A.2 of ISO10993-9, degradation studies are not required if the probable degradation products are the same substances, in similar quantities, and at a similar rate as devices that have a history of safe clinical use | Not Required |
| ISO 10993-15: 2000<br>Degradation of metals/alloys | No evidence of corrosion / dissolution of metals and alloys from the electrodes and conductor coils | Passed |

| Biological Effect per ISO 10993-# | Test Method | Test Result |
|---|---|---|
| ISO 10993-18: 2005<br>Chemical characterization | Profile of extractables/leachable chemicals in the lead was conducted. Identified extractables must be the same substances, in similar quantities, and at a similar rate as devices that have a history of safe clinical use. | Successfully Completed |

**Table 5: Summary of Biocompatibility Testing of Packaging for Lead and Lead Accessories**

| Test Performed | Test Method | Test Result |
|---|---|---|
| ISO 10993-5: 2009<br>In vitro cytotoxicity | Cytotoxicity MEM Elution | Passed |
| USP 32, NF 27 Monograph <661> Physicochemical Tests for Plastics | Extraction using purified water | Passed |

### X.A.2. Bench Testing Not Related to MRI

**Implantable Pulse Generator System Testing Outside the MRI Environment**

The INGENIO™ MRI, VITALIO™ MRI and FORMIO™ MRI pacemakers use the same platform and design as the commercially available INGENIO™, VITALIO™ and FORMIO™ (non-MRI) pacemakers. Likewise the ESSENTIO™ MRI, PROPONENT™ MRI and ACCOLADE™ MRI pacemakers use the same platform and design as the commercially available ESSENTIO™, PROPONENT™ and ACCOLADE™ (non-MRI) pacemakers. For the purpose of this testing the only difference is the unique MR Conditional X-ray Identification (ID) tag used in the MRI models. Therefore, the bench testing outside of the MRI environment performed on the commercially available non-MRI pacemakers applies to the corresponding MRI pacemakers (by family). A brief summary is provided in

**Table** 6.

**Table 6: Summary of Bench Testing Outside the MRI Environment for the Ingenio and Accolade Pacemakers**

| Test Activity | Summary | Results |
|---|---|---|
| Component Testing on new or modified components | Performed qualifications to ensure component suppliers are capable of providing parts that meet Boston Scientific requirements. | Passed |

| Test Activity | Summary | Results |
|---|---|---|
| System Design Testing | Conducted to verify a specific sub-set of system requirements that require end to end testing in the System Requirement Specification (SyRS) and are not otherwise cover by HW (mechanical, electrical and component), SW or FW testing. System under test included PG with PG FW and 2869 PRM SW. | Passed |
| Mechanical Testing | Conducted to verify that the PG meets the mechanical design specifications. Mechanical and environmental requirements were tested. | Passed |
| Electrical Testing | Conducted to verify that the PG meets the electrical design specifications. | Passed |
| PG Software (Firmware) Testing | Conducted to verify the PG FW meets the FW requirements specification. | Passed |
| Model 2869 PRM Software Testing | Conducted to verify the Model 2869 PRM SW meets the SW requirements specification. | Passed |
| Battery Testing | Conducted to verify that the battery meets design performance requirements. Testing verifies battery performance at stress conditions beyond the limits expected for the device / system. | Passed |
| Packaging Testing | Conducted to verify that the packaging system meets all the design requirements after being exposed to challenge conditions (sterilization, climatic conditioning, distribution simulation, aging). | Passed |

**Lead and Lead Accessory Testing Outside the MRI Environment**

The INGEVITY lead is equivalent for testing conducted outside the MRI environment, regardless of lead type between non-MRI and MRI. A brief summary is provided in **Table** 7.

**Table 7: Summary of Bench Testing for the INGEVITY™ Lead and Lead Accessories**

| Test Activity | Summary | Applicable Standards | Results |
|---|---|---|---|
| Component Testing on new or modified components used in the INGEVITY leads or lead accessories | Performed qualifications to ensure component suppliers are capable of providing parts that meet Boston Scientific requirements. | Varies by component/material if applicable | Passed |

| Test Activity | Summary | Applicable Standards | Results |
|---|---|---|---|
| Mechanical and Electrical Testing with Shelf Life Testing | Verified the mechanical and electrical performance of the active and passive fixation designs of the INGEVITY family of leads after accelerated and real time aging representing two years of shelf life. | ASTM D4169-09<br>ISO 14708-1: 2000<br>EN 45502-1: 1997 | Passed |
| Terminal Testing with Shelf Life Testing | Verified the INGEVITY lead terminal mechanical and electrical performance meets the product specification after accelerated and real time aging representing two years of shelf life. | ASTM D4169-09<br>ISO 5841-3<br>ISO 14708-1: 2000<br>EN 45502-1: 1997 | Passed |
| Lead Explant Axial Strength Testing with Shelf Life Testing | Verified the explant axial strength performance of the active and passive fixation INGEVITY lead designs after accelerated and real time aging representing two years of shelf life. | ISO 14708-1: 2000<br>EN 45502-1: 1997 | Passed |
| Packaging and Package Shelf Life Testing | Verified the INGEVITY device packaging meets requirements of package cleanliness, packaging and labeling integrity, packaging and literature materials and sterile tray content, after accelerated and real time aging representing two years of shelf life. | ASTM D4169-09<br>EN 45502-2-1,<br>11607-1:2006,<br>ISO 5841-3<br>ISO 14708-1: 2000<br>EN 45502-1: 1997 | Passed |
| Corrosion Performance Testing | Verified the current induced corrosion performance of the active and passive fixation INGEVITY lead designs. Verify the mechanical, electrical, and corrosion performance of conductor joints at the distal end of the lead after being subjected to an equivalent to 10 years of pacing in an accelerated period in saline. | EN 45502-2-1 and ISO 5841-3<br>ISO 14708-1: 2000<br>EN 45502-1: 1997 | Passed |
| Steroid Testing | Verified the active and passive fixation INGEVITY leads conform to the steroid requirements in the product specification. | USP <788><br>ISO 14708-1: 2000<br>EN 45502-1: 1997 | Passed |

| Test Activity | Summary | Applicable Standards | Results |
|---|---|---|---|
| Lead Distal Section Fatigue Validation Test | Demonstrated the fatigue performance of the conductors in the distal section of the lead in the cyclic bending conditions experienced during 10 years of chronic implant in the right ventricle of the heart. The test demonstrated the distal section of the lead can experience 400 million cycles of intracardiac flexure without conductor fatigue fracture. | ISO 14708-1: 2000<br>EN 45502-1: 1997 | Passed |
| Lead Body Bell-Mouth Fatigue Mechanical Testing | Demonstrated that the uniform lead body region of the INGEVITY lead can experience 64,000 cycles when exposed to the 6-mm bell-mouth test condition established in the CEN-CENELEC International Standard (EN 45502-2-1 Section 23.5, Test 1) without conductor fatigue fracture. | CEN-CENELEC International Standard (EN 45502-2-1)<br>ISO 14708-1: 2000<br>EN 45502-1: 1997 | Passed |
| Subcutaneous Lead Body Fatigue Mechanical Testing | Demonstrated that the INGEVITY lead can experience cyclic deflections equivalent to 10 years of subcutaneous flexure without conductor fatigue fracture. | ISO 14708-1: 2000<br>EN 45502-1: 1997 | Passed |
| Intracardiac Lead Body Fatigue Testing | Demonstrated that the intracardiac region of the INGEVITY lead can experience cyclic deflections equivalent to 10 years of intracardiac flexure without conductor fatigue fracture | ISO 14708-1: 2000<br>EN 45502-1: 1997 | Passed |
| Terminal Flex Fatigue Testing | Demonstrated the IS-1 conductors in the terminal region of the lead can experience the cyclic test conditions established in the CEN-CENELEC International Standard (EN 45502-2-1 Section 23.5, Test 2), with the exception of the tensile load, which was increased from 100g in the CEN-CENELEC standard to 200g. | CEN-CENELEC International Standard (EN 45502-2-1)<br>ISO 14708-1: 2000<br>EN 45502-1: 1997 | Passed |

| Test Activity | Summary | Applicable Standards | Results |
|---|---|---|---|
| **Accessory Testing** | | | |
| Accessory Mechanical/ Electrical and Shelf Life Testing | Verified the slit suture sleeve Model 6402 conforms to the mechanical requirements of handling, retention and lead body protection and meets the requirements of a four year shelf life. | ASTM 4169-09<br>EN 45502-2<br>EN 45502-2-1<br>ISO 14708-1: 2000<br>EN 45502-1: 1997 | Passed |
| Accessory Particulate Testing | Verified the slit suture sleeve Model 6402 conforms to its requirements for product and packaging cleanliness. | ASTM 4169-09<br>EN 45502-2<br>EN 45502-2-1<br>ISO 14708-1: 2000<br>EN 45502-1: 1997 | Passed |
| Accessory Package and Shelf Life Testing | Verified the accessory packaging used for the slit suture sleeve Model 6402 and the stylet accessories performs its intended functions to contain, protect and maintain a sterile barrier for the intended four years of shelf life. Testing also verified the performance of the printed markings of the labeling. | EN ISO 11607-1:2006 | Passed |
| Stylet Accessory Shelf Life Testing | Verified the stylet models for use with INGEVITY leads meet the requirement for a four-year shelf life. | None | Passed |

### X.A.3. Testing Related to MRI

This section provides a summary of the pre-clinical evaluation performed to demonstrate safety and effectiveness of the ImageReady™ MR Conditional Pacing System with respect to MRI-environment hazards. The pre-clinical evaluation included MRI scanner testing, bench testing, computer modeling, and animal studies performed by Boston Scientific as guided by ISO/TS 10974, "Assessment of the safety of magnetic resonance imaging for patients with an active implantable medical device." Boston Scientific's pre-clinical evaluation was designed to: a) apply exposure levels more severe than typically encountered during clinical MRI scanning; b) provide monitoring and measurement methods sensitive enough to detect any possible device performance anomalies; and c) assess a wide range of system implant and patient anatomy configurations. All evaluations were performed under generalized, conservative conditions for patient and device exposure in 1.5T MRI scanners, including conditions beyond limits typically encountered in clinical practice. An MRI scanner was used where appropriate for system-level testing. Standard test methods and test equipment were used where possible. Custom test systems were developed and used to create higher exposure levels as needed in bench and animal testing.

The pre-clinical evaluation demonstrates Boston Scientific MR Conditional pacemakers and leads, when used together, meet all product requirements designed to mitigate the risks associated with MRI scans. These results demonstrate the ImageReady System is safe and effective for scans performed in accordance with the labeled Conditions of Use.

The following testing related to MRI is summarized in **Table 8** through **Table 15** below:

- Lead and PG Heating
- Vibration
- Translation Force
- Torque
- Image Artifact
- Unintended Cardiac Stimulation
- PG Malfunction

**Lead Heating**

**Table 8: Summary of Lead Heating Testing Related to MRI**

| **Lead Heating** | |
|---|---|
| Field Interaction | Radiofrequency |
| Mechanism and Source of Hazard | Pacing leads may act as antennae, picking up RF energy. A portion of this energy may be transmitted into the cardiac tissue and converted into heat. |
| Clinical Impact | Heating near the lead electrodes may cause thermal tissue injury, which may alter pacing thresholds. |
| Evaluation Method | The patient safety risk due to MRI-induced lead heating was evaluated using a combination of bench testing, computer modeling, and animal studies.<br>A computer modeling framework was used to compute the RF power deposited to cardiac tissues in contact with lead electrodes in approximately 0.5 million simulated patient and scanning scenarios. The computer model was developed based on known RF theory and was extensively validated by performing lead heating measurements in an RF coil test system. The 0.5 million simulated scenarios were developed using established electromagnetics simulation methods and are comprised of combinations of human body models, lead implant configurations, and MRI scanner/scanning conditions. Using the computer modeling framework, a worst-case RF power potentially inducible in any patient with INGEVITY MRI leads was determined.<br>An animal study was performed to determine the change in pacing capture threshold as a function of RF power. The worst-case RF power was compared to results of the animal study to assess the risk of clinically significant change in pacing capture threshold caused by MRI-induced lead heating. |

| Lead Heating | |
|---|---|
| Results & Conclusions | Bench testing, computer modeling, and animal study results indicate patient safety risk due to MRI-induced lead heating of the ImageReady™ MR Conditional Pacing System is minimal. Analysis of the results demonstrated that MRI-induced tissue heating around INGEVITY MRI lead electrodes is unlikely to cause a clinically significant change in pacing capture threshold. These results support the safety of ImageReady Systems with regard to the MRI-induced lead heating hazard. |

**PG Heating**

**Table 9: Summary of PG Heating Testing Related to MRI**

| PG Heating | | |
|---|---|---|
| **Field Interaction** | Radiofrequency | Gradient |
| **Mechanism and Source of Hazard** | The PG case concentrates RF electric field into adjacent tissue. | Gradient magnetic fields induce electrical currents in conductive materials of the PG, such as the case and internal components, which are dissipated as heat. |
| **Clinical Impact** | Tissue heating near the PG case may cause patient discomfort or tissue injury. | |
| **Evaluation Method** | The patient safety risk due to MRI-induced PG heating was evaluated through analysis of bench testing and computer modeling. Gradient field induced heating of the PG case was measured in a gradient coil test system. Radiofrequency field induced heating of tissues surrounding the PG was determined using established electromagnetics simulation methods. Both bench testing and computer modeling were performed under worst-case conditions for gradient and RF field exposures. Testing and modeling results were compared to thresholds for tissue damage reported in published literature to assess the risk of clinically significant temperature rise caused by MRI-induced PG heating. | |
| **Results & Conclusions** | Analysis comprised of bench testing and computer modeling indicates patient safety risk due to MRI-induced heating of Ingenio and Accolade PGs is minimal. Testing and modeling demonstrated that heating of and around the pacemaker will not harm surrounding tissues. These results support the safety of the ImageReady™ MR Conditional Pacing System with regard to the MRI-induced PG heating hazard. | |

## Vibration

**Table 10: Summary of Vibration Testing Related to MRI**

| **Vibration** | |
|---|---|
| **Field Interaction** | Static and Gradient |
| **Mechanism and Source of Hazard** | Gradient fields induce electrical currents in the conductive surfaces of pacemaker components. Interaction of these currents with the static magnetic field causes vibration. |
| **Clinical Impact** | Vibration of the PG may cause device malfunction, including loss or alteration of pacing therapy. |
| **Evaluation Method** | Bench testing was performed to evaluate the potential for PG malfunction and damage resulting from MRI-induced vibration. A shaker table based test system was used to apply vibration profiles representative of vibration expected in a pacemaker during MRI scans. Vibration testing was conducted at vibration stress levels above and for durations beyond what a device would reasonably be exposed to during its lifetime. Device functionality testing was performed to ensure normal pacing system operation, including therapy delivery. |
| **Results & Conclusions** | Bench testing confirmed that device malfunction and damage caused by MRI-induced vibration of Ingenio and Accolade PGs are unlikely. No device malfunctions or damage were observed during vibration testing and all devices performed normally after vibration testing. These results support the safety and effectiveness of the ImageReady System with regard to the MRI-induced vibration hazard. |

## Translation Force

**Table 11: Summary of Translation Force Testing Related to MRI**

| **Translation Force** | |
|---|---|
| **Field Interaction** | Static |
| **Mechanism and Source of Hazard** | The static magnetic field will act on any ferromagnetic material in a PG or lead, producing a translation or rotation of the PG or lead. |
| **Clinical Impact** | PG or lead movement may cause patient discomfort, tissue injury, or device dislodgment. |
| **Evaluation Method** | The patient safety risk due to MRI static field induced force was evaluated in bench tests. The MRI induced force exerted on pacemakers and leads was measured using test methods described in ASTM F2052-02, "Standard Test Method For Measurement of Magnetically Induced Displacement Force On Medical Devices in the Magnetic Resonance Environment." |

| Translation Force | |
|---|---|
| **Results & Conclusions** | Bench testing demonstrated that MRI-induced force on Ingenio and Accolade PGs and INGEVITY MRI leads is minimal. These results support the safety of the ImageReady™ MR Conditional Pacing System with regard to the MRI-induced force hazard. |

## Torque

**Table 12: Summary of Torque Testing Related to MRI**

| Torque | |
|---|---|
| **Field Interaction** | Static |
| **Mechanism and Source of Hazard** | The static magnetic field will act on any ferromagnetic material in a PG or lead, producing a torque of the PG or lead. |
| **Clinical Impact** | PG or lead movement may cause patient discomfort, tissue injury, or device dislodgement. |
| **Evaluation Method** | The patient safety risk due to MRI static field induced torque was evaluated in bench tests. The MRI induced torque exerted on pacemakers and leads was measured using test methods described in ASTM F2213-02, "Standard Test Method for Measurement of Magnetically Induced Torque on Passive Implants in the Magnetic Resonance Environment" |
| **Results & Conclusions** | Bench testing demonstrated that MRI-induced torque on Ingenio and Accolade PGs and INGEVITY MRI leads is minimal. These results support the safety of the ImageReady™ MR Conditional Pacing System with regard to the MRI-induced torque hazard. |

## Image Artifact

**Table 13: Summary of Image Artifact Testing Related to MRI**

| Image Artifact | |
|---|---|
| **Field Interaction** | Static, Gradient, and Radiofrequency |
| **Mechanism and Source of Hazard** | The pacing system may interfere with the acquisition of MR data. |
| **Clinical Impact** | Image artifacts may compromise the usefulness of MR images. |
| **Evaluation Method** | MRI scanner testing was performed to evaluate the size of the image artifact produced by the ImageReady System. The image artifact created by pacemakers and leads was measured using test methods described in ASTM F2119-07, "Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants" |

| Image Artifact | |
|---|---|
| **Results & Conclusions** | MRI scanner testing confirmed the appearance of image artifact is consistent with expectation for metallic implanted devices. |

## Unintended Cardiac Stimulation (UCS)

**Table 14: Summary of Unintended Cardiac Stimulation Testing Related to MRI**

| Unintended Cardiac Stimulation | | |
|---|---|---|
| **Field Interaction** | Gradient and Radiofrequency | |
| **Mechanism and Source of Hazard** | Gradient: The time varying gradient field will induce a voltage between the pacing lead electrodes and the PG. Current may conduct from the lead electrodes to the heart. | RF: The time varying RF field will induce a voltage along the pacing leads. The PG circuitry may rectify the voltage and conduct a current to the heart. |
| **Clinical Impact** | MRI-induced currents, if large enough, may directly stimulate the heart. | |
| **Evaluation Method** | The patient safety risk due to MRI-induced UCS was evaluated using a combination of bench testing and animal studies. Bench testing was performed to measure currents potentially induced on the pacing system and injected into tissues resulting from: a) rectification of RF pulses; and b) interactions with gradient fields. An animal study was performed to determine the strength-duration relationship for a current stimulus to capture cardiac tissue. The probability that UCS could occur was determined by comparing the statistical distributions of MRI-induced current obtained in bench testing with statistical distributions of capture thresholds obtained in animals. | |
| **Results & Conclusions** | Bench testing and animal study results indicate patient safety risk due to MRI-induced UCS of the ImageReady™ MR Conditional Pacing System is remote. Analysis of the results demonstrated that the probability for MRI-induced unintended stimulation resulting in cardiac tissue capture is exceedingly small. These results support the safety of the ImageReady System with regard to the MRI-induced UCS hazard. | |

## PG Malfunction

**Table 15: Summary of PG Malfunction Testing Related to MRI**

| PG Malfunction | |
|---|---|
| **Field Interaction** | Static, Gradient, and Radiofrequency |
| **Mechanism and Source of Hazard** | The static, gradient, and RF fields may interfere with the electrical operation of the pacing system. |

| PG Malfunction | |
|---|---|
| **Clinical Impact** | MRI-field interactions may cause PG malfunction, including loss or alteration of pacing therapy. |
| **Evaluation Method** | MRI scanner and bench testing were performed to evaluate the potential for PG malfunction and damage resulting from MRI-field interactions. MRI scanner testing was performed to evaluate pacing system operation during and after exposure to the combination of static, radiofrequency, and gradient fields. Bench testing was performed to evaluate pacing system operation during and after independent exposure to static, radiofrequency, and gradient fields. For bench testing, custom electrical injection test systems and a custom gradient coil system were used to apply exposure levels at or above what a device would reasonably be exposed to in clinical scanning scenarios. Device functionality testing was performed to ensure normal pacing system operation, including therapy delivery. |
| **Results & Conclusions** | MRI scanner and bench testing confirmed device malfunction and damage resulting from MRI-field interactions of ImageReady systems are unlikely. MRI scanner testing confirmed normal pacing system operation, including therapy delivery, during and after exposure to the combination of static, radiofrequency, and gradient fields. Bench testing confirmed normal pacing system operation, including therapy delivery, during and after independent exposure to static, radiofrequency, and gradient fields. No device malfunction or damage was observed during testing and all devices performed normally after MRI scanner and bench testing. These results support the safety and effectiveness of the ImageReady System with regard to the MRI-induced malfunction hazard. |

## X. B. Animal Studies

The safety of the INGEVITY™ leads and ImageReady™ MR Conditional Pacing System was evaluated in a series of canine studies (see **Table 16**); these studies were conducted in accordance with §21 CFR 58 – Good Laboratory Practice (GLP). The results of the studies support the safety of the INGEVITY leads and ImageReady System. System level testing of the Ingenio and Accolade family of pulse generators was done via animal studies conducted in accordance with GLP; these studies were not specific to the MRI versions of Ingenio and Accolade pacemakers and were reviewed by FDA under supplements for existing families of devices.

**Table 16: Summary of GLP Animal Studies**

| Study Name/ Number | Objective | # / Type Animals Test Devices Study Duration | Method | Results |
|---|---|---|---|---|
| Chronic Evaluation of Pacing Capture Threshold (PCT) Change in a Canine Model GLP Study 10-124G | Obtain data to understand the relationship between heating, power dissipation, and Pacing Capture Threshold (PCT) change for the INGEVITY lead family. | • 10 Canines<br>• Test articles consisting of lead outer insulation and distal electrodes with coaxial cable and fiber optic temperature probe<br>• 40 days | Test articles were designed to efficiently transmit RF power to the distal electrodes (actual lead electrode) and allow measurements of PCT, impedance and R-wave amplitudes via the coaxial cable using a pacing system analyzer device.<br>The power dissipation to PCT/temperature change relationship was obtained by measuring changes to PCT and any increases in lead tip-tissue interface temperature that may be caused by delivering RF power to the lead distal electrodes at various power levels. | Sufficient data were collected to establish a relationship between PCT change and RF total dissipated power for the INGEVITY lead family to establish a lead heating performance specification. |

| Study Name/ Number | Objective | # / Type Animals Test Devices Study Duration | Method | Results |
|---|---|---|---|---|
| Passive Fixation Lead Electrical/ Mechanical GLP Study 10-122G | Assess the safety and efficacy of the INGEVITY passive pacing lead system in a canine model over 90 and 180 days post implant.<br>An additional purpose of the study was to gather observational data pertaining to the INGEVITY MRI lead for probability analysis of unintended cardiac stimulation hazard. | • 20 Canines<br>• Model 7632 passive fixation straight lead<br>• Model 7636 passive fixation preformed J lead<br>• 90 days for endpoints and 180 days for observational data | The lead test articles were implanted and connected to a pacemaker. Electrical data (atrial and ventricular pacing voltage threshold, atrial sensing P wave, ventricular sensing R wave) was taken throughout the study to document lead function and radiographs taken to document lead position.<br>Simulated MRI electrical testing was performed on 18 animals to characterize chronic single beat stimulation threshold measurements over the range of gradient and RF field pulse widths for an MR scanner.<br>All animals had a comprehensive necropsy performed, including to inspect and observe gross cardiac changes and to assess the cellular-level tissue biocompatibility response at the implant site. | Under the conditions of this study, the chronic electrical performance endpoints were successfully met and observational data was collected. The study successfully supported safety and efficacy of the INGEVITY passive pacing lead system in a canine model over 90 days post implant and continued to collect observational data up to 180 days post implant.<br>The study successfully collected the single beat stimulation threshold measurements over a range of pulse widths relevant to MR scanners after 90 or 180 days post implant in the canine model. |

| Study Name/ Number | Objective | # / Type Animals Test Devices Study Duration | Method | Results |
|---|---|---|---|---|
| Active Fixation Lead Electrical/ Mechanical GLP Study 10-072G | Assess the safety and efficacy of the INGEVITY active pacing lead system in a canine model over 90 and 180 days post implant.<br>An additional purpose of the study was to gather observational data pertaining to the INGEVITY MRI lead for probability analysis of unintended cardiac stimulation hazard. | • 19 Canines<br>• Model 7642 active fixation straight lead<br>• 90 days for endpoints and 180 days for observational data | The lead test articles were implanted and connected to a pacemaker. Electrical data (atrial and ventricular pacing voltage threshold, atrial sensing P wave, ventricular sensing R wave) was taken throughout the study to document lead function and radiographs taken to document lead position. .<br>Simulated MRI electrical testing was performed on 16 animals to characterize chronic single beat stimulation threshold measurements over the range of gradient and RF field pulse widths for an MR scanner.<br>All animals had a comprehensive necropsy performed, including to inspect and observe gross cardiac changes and to assess the cellular-level tissue biocompatibility response at the implant site. | Under the conditions of this study, the chronic electrical performance endpoints were successfully met and observational data was collected. The study successfully supported safety and efficacy of the INGEVITY Active pacing lead system in a canine model over 90 days post implant and continued to collect observational data up to 180 days post implant.<br>The study successfully collected the single beat stimulation threshold measurements over a range of pulse widths relevant to MR scanners after 90 or 180 days post implant in the canine model. |

| Study Name/ Number | Objective | # / Type Animals Test Devices Study Duration | Method | Results |
|---|---|---|---|---|
| Acute Accessory GLP Study 11-022G | Demonstrate the safety and performance of the INGEVITY active and passive fixation pacing leads with their compatible accessories in an acute setting in an animal model. | • 2 swine<br>• Models 7641 and 7642 active fixation straight leads<br>• Model 7636 passive fixation preformed J lead<br>• Model 7632 passive fixation straight lead<br>• Model 6402 Slit Suture Sleeve<br>• 0.014 inch long tapered straight stylets<br>• 0.013 inch tapered straight stylets<br>• Acute | Standard right atrium (RA) and right ventricle (RV) brady lead implant technique was used for the lead implantation. The lead with stylet was inserted and positioned in the RV chamber, RA chamber or appendage multiple times. A pacing system analyzer (PSA) device was connected to select leads and used to collect electrical data. Fluoroscopy cines were also taken throughout the study to view the lead position and the suture sleeve visibility.<br>Acute repositionability of the lead in the RA and RV and compatibility with accessories were tested in this study. Qualitative data were collected and recorded regarding the ease and general performance of the INGEVITY lead with specified accessories. | Endpoint 1:<br>**PASS**<br>Demonstration that the INGEVITY active fixation straight leads could withstand five consecutive cycles of positioning in the ventricle in ≤ 18 turns for full extension and retraction.<br>Endpoint 2:<br>**PASS**<br>Demonstration that the INGEVITY family of leads were successfully compatible with:<br>• Select stylets<br>• Slit suture sleeves<br>• Introducers (6Fr and 9Fr)<br>• Guide wires<br>Data on five observational criteria was collected. |

| Study Name/ Number | Objective | # / Type Animals Test Devices Study Duration | Method | Results |
|---|---|---|---|---|
| Passive and Active Fixation Lead Drug Characterization GLP Studies 10-073G and 10-074G) | Characterize the drug system of the INGEVITY passive fixation and active fixation pacing/sensing leads | • 15 Canines in the passive fixation lead study<br>• 9 Canines in the active fixation lead study<br>• Model 7632 passive fixation straight lead<br>• Model 7636 passive fixation preformed J lead<br>• Model 7642 active fixation straight lead<br>• Up to 90 days | The animals were implanted with the INGEVITY leads and survived until their predetermined endpoints (2, 7, 14, 21, 28, 44, 60 and 90 days).<br>Plasma samples were collected and analyzed at multiple time points throughout the study to measure circulating DX. Endocardial tissue was collected at the location of each lead drug collar during necropsy and subsequently analyzed to measure tissue concentration of DX. Each lead's drug-containing component was analyzed for residual DXA.<br>Observational data were collected during the in-life phase:<br>• Radiographic or fluoroscopic images<br>• Electrical data at implant and just prior to animal termination<br>• Gross necropsy | An assessment of dexamethasone (DX) drug release following lead implant of the INGEVITY passive and active fixation pacing lead systems in an animal model at prescribed time points through 90 days post implant was completed. Systemic (plasma) dexamethasone (DX) and tissue (endocardium) DX concentrations were measured as well as residual dexamethasone acetate (DXA) in the collars of the explanted leads. The studies provided appropriate characterization data on the drug system of the INGEVITY passive and active fixation pacing/sensing leads (3 samples per time-point), respectively. |

## X. C. Sterilization

The Ingenio and Accolade pulse generators, as well as the INGEVITY leads and lead accessories, are sterilized via Ethylene Oxide (EO) in accordance with internal quality control procedures and ANSI/AAMI/ISO 11135:2007 Medical Device – Validation and Routine Control of Ethylene Oxide Sterilization. Residual testing was conducted per ISO 10993-7:2008 Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals. The validated EO sterilization process has demonstrated Sterility Assurance Levels (SAL) of greater than $10^{-6}$.

## XI. SUMMARY OF PRIMARY CLINICAL STUDY FOR THE LEAD

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of implantation of the INGEVITY Active Fixation and Passive Fixation Pace/Sense Leads for the treatment of the conditions listed in Section II.A in the US and internationally under IDE G110227. Data from this clinical study were the basis for the PMA approval decision, along with data from the SAMURAI study under IDE G120076 (see Section XII for details). A summary of the clinical study is presented below.

### A. Study Design – INGEVITY

Patients were treated between October 22, 2012 and October 22, 2013. Treatment was defined as implanted or attempted with at least one INGEVITY lead. The database for this PMA reflected data collected through February 17, 2016 and included 1060 patients and 1599 leads. There were 43 US and 34 international investigational sites.

The INGEVITY Study is a prospective, single-group, non-randomized, multi-center, global clinical study, utilizing performance goals to demonstrate the safety, performance and effectiveness of the INGEVITY Leads. As a single-group study, there was no control group in the INGEVITY study.

The study used a Clinical Events Committee as a group of independent evaluators to adjudicate mortality.

The INGEVITY Study has been conducted through the 12-month follow-up endpoints to collect data to support US pre-market approval of the INGEVITY lead family. Data continues to be collected via annual follow-up at 2 through 5 years in support of post-market approval requirements.

To appropriately characterize long-term safety performance of this new family of pace/sense leads, the various leads in the INGEVITY lead family are studied in separate "lead cohorts." The right ventricular active fixation lead serves as the primary lead model in the INGEVITY Study, and therefore is studied as lead cohort 1 with a sample size equal to 700 leads evaluable at 12 months. The required sample sizes for the right atrial active fixation lead, the right ventricular passive fixation lead and the right atrial passive fixation lead are 350, 175, and 35 leads, respectively,

evaluable at 12 months. The following lead cohorts were studied in the INGEVITY Study:

- Lead Cohort 1 = Right ventricular active fixation leads
- Lead Cohort 2 = Right atrial active fixation leads
- Lead Cohort 3 = Right atrial and right ventricular passive fixation leads

Subjects were followed in the INGEVITY study based on the date of their INGEVITY Lead implant(s). Follow-up was required at pre-discharge, 1 month, 3 months and 12 months post-implant. Subjects will continue to be followed annually until 5 years post-implant.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the INGEVITY study was limited to patients who met all of the following inclusion criteria:

- Willing and capable of providing informed consent;
- INGEVITY™ Lead(s) and a Boston Scientific pulse generator must be the initial (de novo) pacing system implants for the patient;
- Has a Class I or II indication for implantation of a single (VVI(R) only) or dual chamber pacemaker or CRT-P system according to the American College of Cardiology (ACC)/American Heart Association (AHA)/Hearth Rhythm Society (HRS)[9], or European Society of Cardiology (ESC)[10] guidelines;
- Willing and capable of participating in all testing/visits associated with this clinical study at an approved clinical study center and at the intervals defined by this protocol; and
- Age 18 or above, or of legal age to give informed consent specific to state and national law.

Patients were not permitted to enroll in the INGEVITY study if they met any of the following exclusion criteria:

- Has or has had any pacing or ICD system implants;
- Intended to receive an AAI(R) pulse generator;
- Known or suspected sensitivity to dexamethasone acetate (DXA);

[9] Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) Developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons Circulation 2008;117: e350-e408.

[10] Vardas PE, Auricchio A, Blanc J, et al. Guidelines for cardiac pacing and cardiac resynchronization therapy: The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. Europace 2007; 9: 959-998.

- Has a mechanical tricuspid heart valve;
- Enrolled in any other concurrent study, with the exception of local mandatory governmental registries and observational studies/registries that are not in conflict;
- Documented permanent or persistent AF[11] where the physician intends to implant a dual chamber pulse generator (single chamber VVIR pulse generators are acceptable);
- Currently on the active heart transplant list;
- Documented life expectancy of less than 12 months;
- Women of childbearing potential who are or might be pregnant at the time of study enrollment or INGEVITY™ Lead implant (method of assessment upon physician's discretion); and/or
- Currently requiring dialysis.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at pre-discharge (3-72 hours post-implant), 1, 3, 12, 24, 36, 48 and 60-months postoperatively.

Preoperative and postoperative evaluations and objective parameters measured are listed in the following table. Adverse events and complications were required per the protocol to be reported at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

**Table 17: Data Collection Schedule**

| Procedure/ Assessment | Enroll-ment | Implant | Pre-Discharge | 1 Month | 3 Months | 12 Months | 2, 3, 4, 5 years | Add'l Visits |
|---|---|---|---|---|---|---|---|---|
| **Timeframe** | ≤ 30 days prior to Implant | Day 0[1] | 3-72 h[1] | 30 ± 7 d[1] Clinic Visit | 91±14 d[1] Clinic Visit | 365 ± 45 d[1] Clinic Visit | -2 yr: 730±90 d[1]<br>-3 yr: 1095±90 d[1]<br>-4 yr: 1461±90 d[1]<br>-5 yr: 1826±90 d[1]<br>Clinic Visit | Not specified |
| Informed consent form, including informed consent signature date | **X** | -- | -- | -- | -- | -- | -- | -- |
| Demographics, including age at implant, gender | **X** | -- | -- | -- | -- | -- | -- | -- |
| Physical assessment, including weight and height | **X** | -- | -- | -- | -- | -- | -- | -- |
| Medical history | **X** | -- | -- | -- | -- | -- | -- | -- |
| PSA measurements for all INGEVITY Leads (capture | -- | **X** | -- | -- | -- | -- | -- | -- |

[11] Calkins H, et al. HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. Heart Rhythm 4:816-861, 2007

| Procedure/ Assessment | Enroll-ment | Implant | Pre-Discharge | 1 Month | 3 Months | 12 Months | 2, 3, 4, 5 years | Add'l Visits |
|---|---|---|---|---|---|---|---|---|
| thresholds @ 0.5ms) | | | | | | | | |
| PA and lateral chest X-ray and/or fluoroscopic image of INGEVITY Lead distal tip fixation | -- | X | | -- | -- | -- | -- | -- |
| Implant Questionnaire | -- | X | -- | -- | -- | -- | -- | -- |
| Cardiovascular Medications, including updates and changes | X | X | X | X | X | X | X | O |
| IPG lead measurements for all INGEVITY Leads (threshold @ 0.5ms through 3-Month Visit) | -- | X | X | X | X | X | X | X (if lead-related AE), else O |
| ECG documenting LOC | -- | X | X | X | X | X | X | X (if lead-related AE), else O |
| Adverse Event assessment/ reporting | X | X | X | X | X | X | X | X |
| Protocol Deviation | X | X | X | X | X | X | X | X |

**Legend:** **X** = Required; **--** = Not required/ Not applicable; **O** = Optional; h = hours; d = days; ECG = Electrocardiogram; LOC = Loss of Capture; IPG = Implantable Pulse Generator; PSA = Pacing System Analyzer; PA = Posterior-Anterior

[1] Clock starts after end of Implant procedure, day of implant is day 0 and hour 0 is pocket closure

The follow-up compliance for all successfully implanted subjects is presented in **Table 18**. Follow-up is ongoing.

**Table 18: Follow-Up Visit Compliance** *(N = 1038 Implanted Subjects)*

| Visit | Visit Window | Expected Number of Visits* | Completed Number (%) of Visits | Completed Number (%) of Visits in Visit Window |
|---|---|---|---|---|
| Implant | Not applicable | 1038 | 1038 (100%) | 1038 (100%) |
| Predischarge | 3-72 hours after implant | 1038 | 1037 (99.9%) | 1035 (99.7%) |
| 1 Month Follow-Up | 30 ± 7 days after implant | 1033 | 1015 (98.3%) | 924 (89.4%) |
| 3 Month Follow-Up | 91 ± 14 days after implant | 1018 | 1000 (98.2%) | 916 (90.0%) |
| 12 Month Follow-Up | 365 ± 45 days after implant | 979 | 948 (96.8%) | 912 (93.2%) |
| * Expected number of visits based on the number of subjects actively followed at the time of the opening of the visit window. | | | | |

3. Clinical Endpoints

*SAFETY ENDPOINTS*

With regard to safety, the following endpoints were evaluated for the INGEVITY Leads, to satisfy worldwide regulatory requirements.

- Safety Endpoint 1: Lead-related Complication-Free Rate from Implant through Three Months Post-Implant
- Safety Endpoint 2: Lead-related Complication-Free Rate from Three Months Post-Implant through Twelve Months Post-Implant
- Safety Endpoint 3: Hazard of Lead-Related Complications Over Time

Lead-related complications are defined as lead-related adverse events resulting in permanent loss of pacing therapy, invasive intervention, injury or death. Lead-related adverse events include, but are not limited to the following, based on the Advamed Industry Guidance for Uniform Reporting of Clinical Performance of Cardiac Rhythm Management of Pulse Generators and Leads, and in accordance with the FDA Guidance:

- Cardiac perforation requiring surgical intervention
- Cardiac perforation not requiring surgical intervention
- Conductor fracture/helix damage
- Lead dislodgment
- Failure to capture
- Oversensing
- Failure to sense (undersensing)
- Insulation breach
- Abnormal pacing impedance
- Extracardiac stimulation

Lead-related complications associated with attempted INGEVITY Lead implants counted toward the safety endpoints. Lead-related adverse events that are not a complication counted as a complication if intravenous (IV) drug therapy was necessary to treat the event. IV drug therapy that occured concomitant but unrelated to the lead-related adverse event did not count as a lead-related complication. Complications involving an INGEVITY lead that occurred as a result of a procedure unrelated to that INGEVITY lead did not count toward this safety endpoint. Two examples of this scenario are 1) an INGEVITY lead dislodgment that resulted from an ablation procedure and 2) an RV INGEVITY lead dislodgment that resulted from a repositioning of an RA lead (INGEVITY or market-released).

*EFFECTIVENESS ENDPOINTS*

With regard to effectiveness, the following endpoints were evaluated for the INGEVITY Leads. These endpoints were analyzed separately by lead fixation type and chamber.

- Effectiveness Endpoint 1: Pacing Threshold at 0.5 ms pulse width at Three Months Post-Implant
- Effectiveness Endpoint 2: Sensed Amplitude at Three Months Post-Implant
- Effectiveness Endpoint 3: Pacing Impedance at Three Months Post-Implant

*SUCCESS/FAILURE CRITERIA*

With regard to success/failure criteria, the study was required to pass Safety Endpoints 1, 2 and 3 and Effectivenss Endpoints 1, 2 and 3.

## B. Accountability of PMA Cohort

At the time of database lock, a total of 1060 subjects were enrolled in the PMA study at 77 at 77 centers, including 603 (56.9%) enrollments at 43 centers in the US and 457 (43.1%) (43.1%) enrollments at 34 centers outside of the US., as shown in

**Table** 19.

**Table 19: Enrollment Numbers by Country** *(N = 1060 Enrolled Subjects)*

| Country | Number (%) of Centers | Number (%) of Subjects |
|---|---|---|
| United States | 43 (55.8%) | 603 (56.9%) |
| Spain | 4 (5.2%) | 88 (8.3%) |
| France | 2 (2.6%) | 57 (5.4%) |
| Austria | 3 (3.9%) | 45 (4.2%) |
| United Kingdom | 3 (3.9%) | 39 (3.7%) |
| Germany | 4 (5.2%) | 37 (3.5%) |
| Portugal | 2 (2.6%) | 32 (3.0%) |
| Denmark | 2 (2.6%) | 26 (2.5%) |
| Malaysia | 2 (2.6%) | 25 (2.4%) |
| Belgium | 2 (2.6%) | 22 (2.1%) |
| Italy | 1 (1.3%) | 21 (2.0%) |
| Canada | 3 (3.9%) | 20 (1.9%) |
| Sweden | 2 (2.6%) | 16 (1.5%) |
| Hong Kong | 1 (1.3%) | 11 (1.0%) |
| Thailand | 1 (1.3%) | 10 (0.9%) |
| Australia | 2 (2.6%) | 8 (0.8%) |
| **Total** | **77** | **1060** |

Of the 1060 enrolled subjects, 1038 were successfully implanted with the INGEVITY leads. Subjects were allowed to contribute both a right atrial and a right ventricular lead to the endpoint analyses. There were 563 subjects that contributed both a right atrial lead and a right ventricular lead to the endpoint analyses, and 473 subjects that contributed one lead to the analysis, either a right atrial or a right ventricular lead. **Figure 6** shows the disposition of subjects in the study. A subject could miss a

follow-up visit, and still contribute data at a subsequent follow-up visit. 91% (962) of patients were under follow-up and therefore available for analysis at the 12 month post-operative visit.

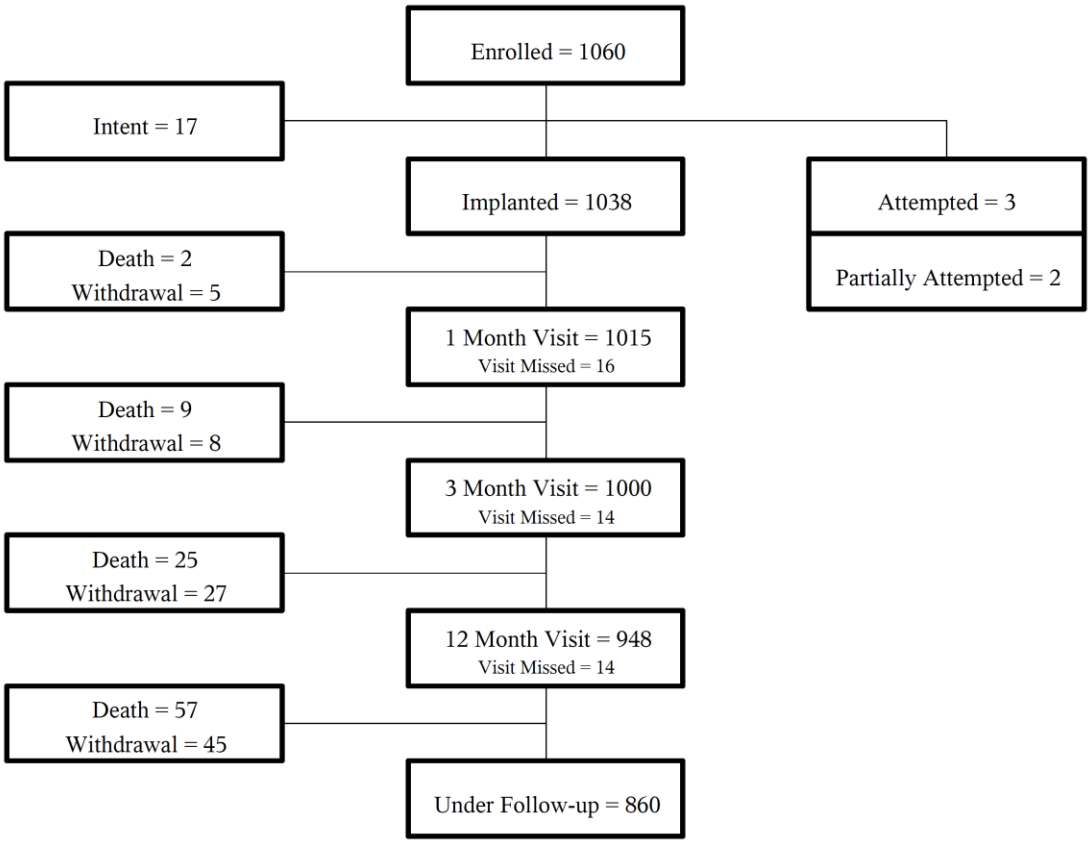


**Figure 6: Subject Disposition**

The last 12-month follow-up visit was performed in November 2014. Results include any visit or event that occurred on or before February 17, 2016. This dataset represents the data submitted in support of the PMA; however, subject follow-up continued beyond this date, with subjects and leads followed for a median of 31 and 32 months, respectively.

*DATA CONTRIBUTING TO ENDPOINTS*

Of the 1060 enrolled subjects, 1599 leads in 1036 subjects were eligible to contribute to endpoint analyses. To be eligible for endpoint analysis the lead must have been the final lead implanted or attempted in a chamber during the intitial implantation procedure. Each patient could contribute up to two leads, one per chamber. **Table 20** summarizes the data contributing to each of the endpoints.

**Table 20: Summary of Data Contributing to Study Endpoints**

| | | Included in Endpoint Analysis | |
|---|---|---|---|
| **Endpoint** | **Description** | **Patients** | **Leads** |
| Safety Endpoint 1 | Lead-Related Complcation-Free Rate through 3 months | 1036 (100%) | 1599 (100%) |
| Safety Endpoint 2 | Lead-Related Complcation-Free Rate from 3 months through 12 months | 1009 (97%) | 1545 (97%) |
| Safety Endpoint 3 | Weibull Shape Parameter for Lead-Related Complications | 1036 (100%) | 1599 (100%) |
| Effectiveness Endpoint 1 | Pacing Threshold @ 0.5 ms at 3 months | 982 (95%) | 1482 (93%) |
| Effectiveness Endpoint 2 (RA) | Sensed Amplitude at 3 months (RA) | 521 (93%) | 521 (93%) |
| Effectiveness Endpoint 2 (RV) | Sensed Amplitude at 3 months (RV) | 914 (88%) | 914 (88%) |
| Effectiveness Endpoint 3 | Pacing Impedance at 3 months | 995 (96%) | 1526 (95%) |

Statistical analyses were performed and determined that the missing/excluded data were highly unlikely to affect the conclusions from the study.

## C. Study Population Demographics and Baseline Parameters

Although the study was performed globally, the demographics of the study population are typical for a pace/sense lead study performed in the US.

Baseline characteristics, including subject demographics and the primary indication for implant for successfully randomized subjects are summarized in **Table 21** and **Table 22**.

**Table 21: INGEVITY Subject Demographics**

| | | | Implanted or Attempted Subjects | |
|---|---|---|---|---|
| **Characteristic** | **Measurement** | **All Enrolled Subjects (N=1060)** | **Pacemaker (N=1006)** | **CRT-P (N=35)** |
| Pulse Generator [N (%)] | Single Chamber Pacemaker | 176 (17) | 176 (17) | 0 (0) |
| | Dual Chamber Pacemaker | 830 (78) | 830 (83) | 0 (0) |
| | CRT-P | 35 (3) | 0 (0) | 35 (100) |
| | No Device | 19 (2) | 0 (0) | 0 (0) |
| Age at Implant (years) | N | 1060 | 1006 | 35 |
| | Mean ± SD | 74.3 ± 10.6 | 74.3 ± 10.5 | 74.5 ± 13.4 |
| | Range | 23.0 - 98.0 | 23.0 - 98.0 | 24.0 - 88.0 |
| Gender [N (%)] | Male | 582 (55) | 554 (55) | 20 (57) |
| | Female | 478 (45) | 452 (45) | 15 (43) |

| | | | Implanted or Attempted Subjects | |
|---|---|---|---|---|
| **Characteristic** | **Measurement** | **All Enrolled Subjects (N=1060)** | **Pacemaker (N=1006)** | **CRT-P (N=35)** |
| Race [N (%)] | Caucasian | 865 (89) | 816 (89) | 31 (100) |
| | Asian | 46 (5) | 46 (5) | 0 (0) |
| | Black, of African heritage | 31 (3) | 30 (3) | 0 (0) |
| | Hispanic or Latino | 13 (1) | 13 (1) | 0 (0) |
| | Not disclosed | 4 (0) | 4 (0) | 0 (0) |
| | Other | 10 (1) | 10 (1) | 0 (0) |
| NYHA Class [N (%)] | I | 138 (37) | 136 (40) | 1 (3) |
| | II | 149 (40) | 137 (41) | 12 (39) |
| | III | 44 (12) | 27 (8) | 16 (52) |
| | IV | 3 (1) | 1 (0) | 2 (6) |
| | No-HF Subject | 39 (10) | 36 (11) | 0 (0) |
| LVEF (%) | N | 812 | 765 | 34 |
| | Mean ± SD | 57.4 ± 10.4 | 58.6 ± 8.9 | 31.8 ± 10.2 |
| | Range | 15.0 - 85.0 | 20.0 - 85.0 | 15.0 - 55.0 |
| QRS Duration (ms) | N | 957 | 908 | 34 |
| | Mean ± SD | 111 ± 28 | 110 ± 28 | 140 ± 29 |
| | Range | 55 - 261 | 55 - 261 | 85 - 202 |
| Body Mass Index ($kg/m^2$) | N | 1052 | 1000 | 35 |
| | Mean ± SD | 28.5 ± 6.5 | 28.5 ± 6.4 | 29.2 ± 5.4 |
| | Range | 10.7 - 105.3 | 10.7 - 105.3 | 19.4 - 43.9 |
| Body Surface Area ($m^2$) | N | 1052 | 1000 | 35 |
| | Mean ± SD | 1.9 ± 0.3 | 1.9 ± 0.3 | 2.0 ± 0.3 |
| | Range | 1.2 - 3.1 | 1.2 - 3.1 | 1.4 - 2.7 |
| Medications* [N (%)] | ACE Inhibitor | 354 (36) | 332 (36) | 17 (49) |
| | Angiotensin Receptor Blocker | 225 (23) | 214 (23) | 9 (26) |
| | ACE Inhibitor and/or Angiotensin Receptor Blocker | 567 (58) | 534 (57) | 26 (74) |
| | Antiarrhythmic | 131 (13) | 122 (13) | 4 (11) |
| | Anticoagulant | 372 (38) | 348 (37) | 18 (51) |
| | Antiplatelet | 454 (46) | 424 (46) | 22 (63) |
| | Diuretics | 461 (47) | 429 (46) | 24 (69) |
| | Beta Blockers | 373 (38) | 341 (37) | 29 (83) |

| | | | Implanted or Attempted Subjects | |
|---|---|---|---|---|
| **Characteristic** | **Measurement** | **All Enrolled Subjects (N=1060)** | **Pacemaker (N=1006)** | **CRT-P (N=35)** |
| | Sodium Channel Blocker | 9 (1) | 9 (1) | 0 (0) |
| | Potassium Channel Blockers | 10 (1) | 10 (1) | 0 (0) |
| | Calcium Channel Blockers | 305 (31) | 298 (32) | 4 (11) |
| | Other Meds | 486 (50) | 460 (50) | 20 (57) |
| Etiology [N (%)] | No Disease (e.g. age related) | 839 (79) | 820 (82) | 5 (14) |
| | Ischemic Cardiomyopathy | 113 (11) | 103 (10) | 9 (26) |
| | Valvular Cardiomyopathy | 39 (4) | 35 (3) | 4 (11) |
| | Idiopathic Cardiomyopathy | 37 (3) | 21 (2) | 15 (43) |
| | Congenital Heart Disease | 16 (2) | 16 (2) | 0 (0) |
| | Hypertrophic Cardiomyopathy | 14 (1) | 11 (1) | 2 (6) |
| Atrial Arrhythmia History* [N (%)] | Paroxysmal Atrial Fibrillation | 277 (25) | 264 (25) | 8 (21) |
| | Permanant Atrial Fibrillation | 107 (10) | 104 (10) | 3 (8) |
| | Atrial Tachycardia/Flutter | 102 (9) | 92 (9) | 7 (18) |
| | Persistent Atrial Fibrillation | 55 (5) | 49 (5) | 4 (10) |
| | None | 560 (51) | 534 (51) | 17 (44) |
| Brady Arrhythmia History* [N (%)] | Sinus Node Dysfunction | 475 (28) | 464 (29) | 2 (4) |
| | Bradycardia | 383 (23) | 372 (23) | 7 (15) |
| | 2nd Degree AV Block - Intermittent | 137 (8) | 131 (8) | 5 (11) |
| | 1st Degree AV Block | 122 (7) | 116 (7) | 6 (13) |
| | 3rd Degree AV Block - Intermittent | 113 (7) | 108 (7) | 2 (4) |
| | 3rd Degree AV Block - Permanent | 107 (6) | 103 (6) | 2 (4) |
| | Chronotropic Incompetance | 46 (3) | 46 (3) | 0 (0) |
| | 2nd Degree AV Block - Permanent | 43 (3) | 43 (3) | 0 (0) |
| | Sinus Arrest | 43 (3) | 43 (3) | 0 (0) |
| | Other | 171 (10) | 157 (10) | 9 (20) |
| | None | 50 (3) | 36 (2) | 13 (28) |
| Associated Diseases and Risk Factors* [N (%)] | Hypertension | 805 (77) | 764 (77) | 27 (77) |
| | Diabetes | 332 (32) | 319 (32) | 10 (29) |
| | Renal Disease | 135 (13) | 127 (13) | 5 (14) |
| | Chronic Pulmonary Disease | 104 (10) | 98 (10) | 5 (14) |

| | | | Implanted or Attempted Subjects | |
|---|---|---|---|---|
| **Characteristic** | **Measurement** | **All Enrolled Subjects (N=1060)** | **Pacemaker (N=1006)** | **CRT-P (N=35)** |
| | Other | 414 (39) | 398 (40) | 13 (37) |
| | None | 126 (12) | 119 (12) | 5 (14) |
| * Subjects may contribute to more than one category | | | | |

**Table 22: Primary CRT-P and Pacemaker Indications** *(N = 35 CRT-P Subjects and N=1006 Pacemaker Subjects)*

| Primary Indication | Number of Subjects |
|---|---|
| **Primary CRT-P Indication** | |
| Severe Systolic Heart Failure | 22 (62.9%) |
| Obstructive Hypertrophic Cardiomyopathy | 1 (2.9%) |
| Other | 12 (34.3%) |
| **Primary Brady Indication** | |
| Sinus Node Dysfunction | 440 (43.7%) |
| 3rd Degree AV Block | 195 (19.4%) |
| 2nd Degree AV Block | 139 (13.8%) |
| Bradycardia, not otherwise specified | 51 (5.1%) |
| Other Block (i.e. Chronic Bifascicular Block) | 45 (4.5%) |
| Tachycardia/Bradycardia Syndrome | 43 (4.3%) |
| Atrial Fibrillation/Flutter with Slow Ventricular Response | 42 (4.2%) |
| 1st Degree AV Block | 28 (2.8%) |
| Neurocardiogenic Syncope | 8 (0.8%) |
| Carotid Sinus Syndrome | 5 (0.5%) |
| Chronotropic Incompetence | 5 (0.5%) |
| Other AV Nodal Block | 2 (0.2%) |
| Other | 3 (0.3%) |
| **Total** | **1041** |

## D. Safety and Effectiveness Results – INGEVITY

### 1. Safety Results

The analysis of safety was based on the evaluation of:

a) key safety outcomes (Safety Endpoints 1, 2 and 3) among 1599 leads eligible for endpoint analysis;
b) adverse events among 1041 patients implanted or attempted with at least one INGEVITY lead; and
c) deaths among 1060 enrolled patients.

To be eligible for endpoint analysis the lead must have been the final lead implanted or attempted in a chamber during the intitial implantation procedure. Each patient could contribute up to two leads, one per chamber. The available timeframe of the analysis is discussed under each endpoint below. The key safety outcomes for this study are presented below in **Tables 23** to **25**. Adverse events (adverse effects) and deaths are reported in **Tables 26** and **27**.

All three safety endpoints were met and are described in detail later in this section.

*SAFETY ENDPOINT 1 – LEAD-RELATED COMPLICATION-FREE RATE FROM 0 TO 3 MONTHS*

The analysis of Safety Endpoint 1 was based on the full cohort of 1599 leads eligible for endpoint analysis. Safety of the INGEVITY lead was evaluated by the lead-related complication-free rate (CFR) from lead implant through the 3-month post-implant follow-ups, with a performance goal of >91.4%. The CFR from 0 through 3 months for all INGEVITY leads was 98.4%, with a one-sided 95% lower confidence limit of 97.7% (see **Figure 7** and **Table 23**).

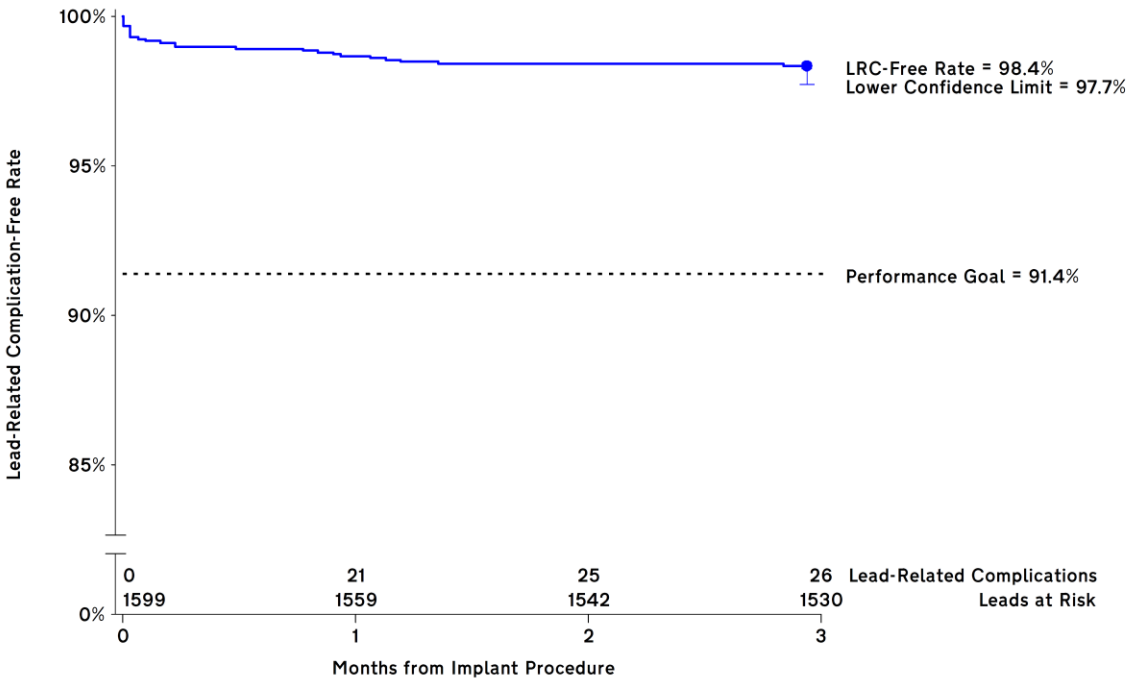


**Figure 7: Safety Endpoint 1 Results – Complication-Free Rate from 0 to 3 Months**

The results were further analyzed by lead cohort (see **Table 23**).

**Table 23: Safety Endpoint 1 Results by Lead Cohort – INGEVITY Lead-Related Complication-Free Rate from 0 to 3 Months**

| Group | Leads at Risk | Leads with a Lead-Related Complication | Lead-Related Complication Free Rate | 95% One-Sided Lower Confidence Limit |
|---|---|---|---|---|
| **All Leads** | **1599** | **26** | **98.4%** | **97.7%** |
| - Lead Cohort 1: RV Active Fixation | 828 | 12 | 98.5% | 97.7% |
| - Lead Cohort 2: RA Active Fixation | 442 | 7 | 98.4% | 97.0% |
| - Lead Cohort 3: RA/RV Passive Fixation | 329 | 7 | 97.9% | 96.1% |

Since the lower confidence limit was greater than the performance goal of 91.4% for all groups, the data support the safety of the INGEVITY lead through the 3-month post-implant period.

*SAFETY ENDPOINT 2 - LEAD-RELATED COMPLICATION-FREE RATE FROM THREE MONTHS POST-IMPLANT THROUGH TWELVE MONTHS POST-IMPLANT.*

The analysis of Safety Endpoint 2 was based on the cohort of 1545 leads eligible for endpoint analysis that also achieved three months of follow-up. Safety of the INGEVITY lead was evaluated by the lead-related complication-free rate (CFR) from 3 months post-implant through 12 months post-implant, with a performance goal of >94%. The CFR from 3 through 12 months for all INGEVTIY leads was 99.7%, with a one-sided 95% lower confidence limit of 99.4 % (see **Figure 8** and **Table 24**).

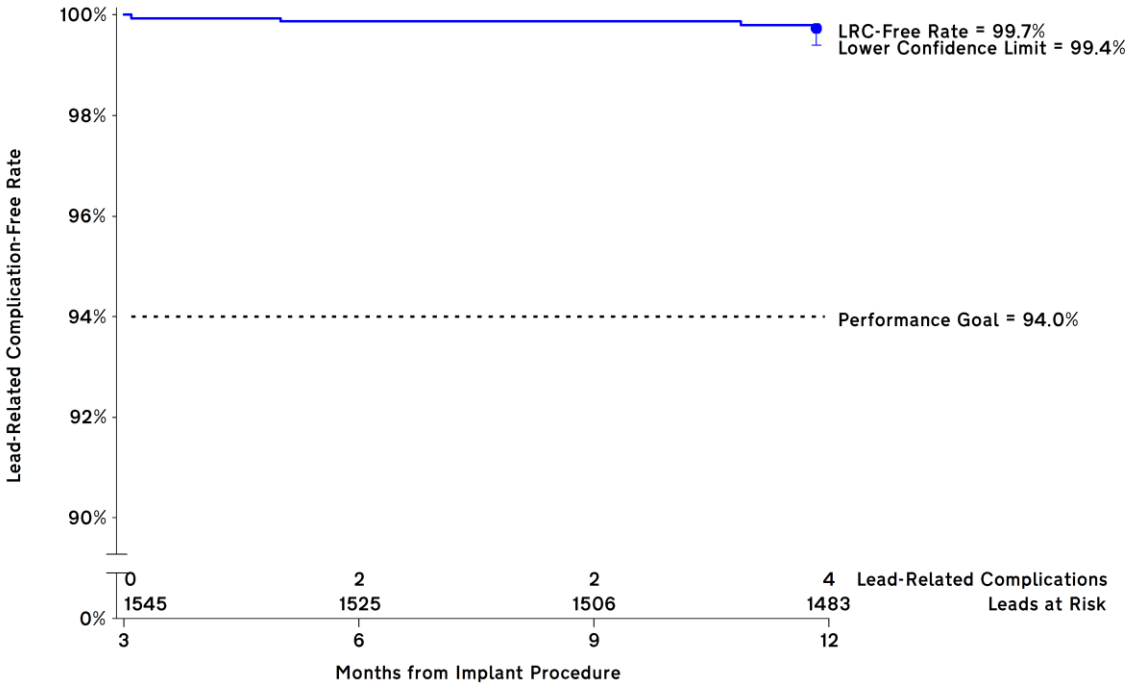


**Figure 8: Safety Endpoint 2 Results – Complication-Free Rate from 3 through 12 Months**

The results were further analyzed by lead cohort (see **Table 24**).

**Table 24: Safety Endpoint 2 Results by Lead Cohort – INGEVITY Lead-Related Complication-Free Rate from 3 through 12 Months**

| Group | Leads at Risk | Leads with a Lead-Related Complication | Lead-Related Complication Free Rate | 95% One-Sided Lower Confidence Limit |
|---|---|---|---|---|
| **All Leads** | **1545** | **4** | **99.7%** | **99.4%** |
| - Lead Cohort 1: RV Active Fixation | 804 | 4 | 99.5% | 98.8% |
| - Lead Cohort 2: RA Active Fixation | 424 | 0 | 100.0% | 100.0% |
| - Lead Cohort 3: RA/RV Passive Fixation | 317 | 0 | 100.0% | 100.0% |

Since the lower confidence limit was greater than the performance goal of 94% for all groups, the data support the safety of the INGEVITY lead through the 12-month post-implant period.

*SAFETY ENDPOINT 3: HAZARD OF LEAD-RELATED COMPLICATIONS OVER TIME*

The analysis of Safety Endpoint 3 was based on the cohort of 1599 leads eligible for endpoint analysis. The hazard of lead-related complications from implant through the entire follow-up period was analyzed by Weibull regression analysis. A Weibull shape greater than one (>1), equal to one (=1) and less than one (<1) indicates accelerating, constant, and decelerating hazard over time, respectively.

The performance goal for this endpoint is a Weibull shape less than one (<1), indicative of a decelerating hazard. The exact follow-up time in the post-implant period for each lead was included in the analysis.

The hazard rate of lead-related complications has been significantly decreasing with time (i.e., decelerating), as evidenced by the Weibull shape parameter equal to 0.23 with a corresponding one-sided 95% upper confidence limit equal to 0.30 (see **Figure 9** and **Table 25**). The figure presents the smooth modeled Weibull hazard resulting from the Weibull regression analysis overlayed on top of the raw observed lead-related complication hazard data.

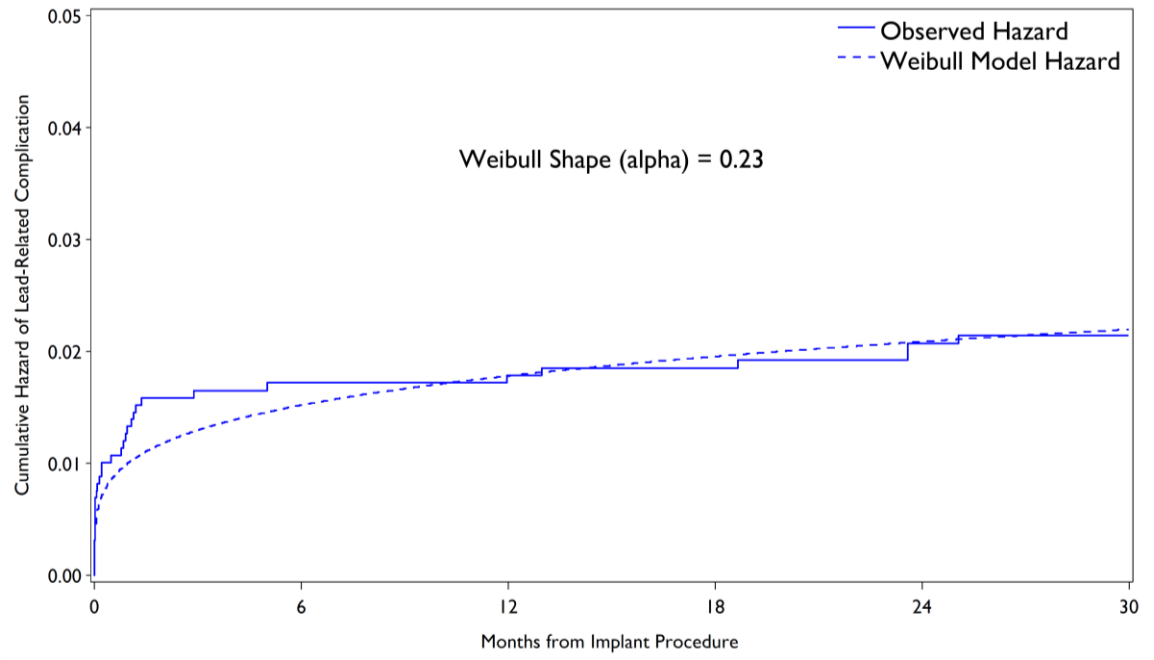


**Figure 9: Safety Endpoint 3 Results – Hazard of Lead-related Complications Over Time**

The results were further analyzed by lead cohort (see **Table 25**).

**Table 25: Safety Endpoint 3 Results by Lead Cohort – Hazard of Lead-related Complications Over Time**

| Group | Weibull Shape Parameter (Alpha) | 95% One-Sided Upper Confidence Limit |
|---|---|---|
| **All Leads** | **0.23** | **0.30** |
| - Lead Cohort 1: RV Active Fixation | 0.24 | 0.35 |
| - Lead Cohort 2: RA Active Fixation | 0.32 | 0.54 |
| - Lead Cohort 3: RA/RV Passive Fixation | 0.15 | 0.28 |

Since the hazard of lead-related complications decelerated over the course of the follow-up period, the data support the safety of the INGEVITY lead.

**Adverse effects that occurred in the PMA clinical study – INGEVITY**

There have been no reported unanticipated adverse device effects in the study as of February 17, 2016. Of the 1041 implanted or attempted subjects, 92.2% were free from adverse events related to the implant procedure; 95.4% and 97.7% were free from adverse events related to the INGEVITY RA and RV leads, respectively.

**Table 26** provides a summary of all Adverse Events reported in the INGEVITY study. See **Section XIII.B. Summary of the Lead-Related Adverse Event Data Collected Across the INGEVITY and SAMURAI Studies** for a summary of adverse events related to the INGEVITY lead.

**Table 26: INGEVITY Study Adverse Events Summary**

| Relationship | Total | | Classification | | | |
|---|---|---|---|---|---|---|
| | | | Complication | | Observation | |
| | Events | N (%) | Events | N (%) | Events | N (%) |
| RA Lead - INGEVITY-related (N at risk = 564) | 27 | 26 (4.6%) | 14 | 14 (2.5%) | 13 | 12 (2.1%) |
| RV Lead - INGEVITY-related (N at risk = 1041) | 31 | 24 (2.3%) | 23 | 16 (1.5%) | 8 | 8 (0.8%) |
| RA Lead - Other (N at risk = 858) | 16 | 15 (1.7%) | 10 | 10 (1.2%) | 6 | 6 (0.7%) |
| RV Lead - Other (N at risk = 1041) | 1 | 1 (0.1%) | 1 | 1 (0.1%) | 0 | 0 (0.0%) |
| LV Lead (N at risk = 47) | 9 | 8 (17.0%) | 1 | 1 (2.1%) | 8 | 7 (14.9%) |
| PG (N at risk = 1041) | 47 | 41 (3.9%) | 9 | 8 (0.8%) | 38 | 33 (3.2%) |
| Procedure (N at risk = 1041) | 92 | 81 (7.8%) | 28 | 27 (2.6%) | 64 | 57 (5.5%) |
| Cardiovascular - HF (N at risk = 1041) | 237 | 140 (13.4%) | 148 | 95 (9.1%) | 89 | 72 (6.9%) |
| Cardiovascular - Non-HF (N at risk = 1041) | 1046 | 528 (50.7%) | 217 | 166 (15.9%) | 829 | 462 (44.4%) |
| Non-cardiovascular (N at risk = 1041) | 1783 | 542 (52.1%) | 666 | 342 (32.9%) | 1114 | 418 (40.2%) |
| Other (N at risk = 1041) | 157 | 129 (12.4%) | 33 | 32 (3.1%) | 124 | 103 (9.9%) |
| Unclassified (N at risk = 1041) | 18 | 17 (1.6%) | 0 | 0 (0.0%) | 0 | 0 (0.0%) |
| **Total (N at risk = 1041)** | **3464** | **789 (75.8%)** | **1150** | **497 (47.7%)** | **2293** | **673 (64.6%)** |

**Device Deficiencies Summary**

The INGEVITY study and the SAMURAI study each collected device deficiencies. Per ISO 14155, a device deficiency was defined as any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling. Per ISO 14155, device deficiencies and adverse events have unique definitions. Therefore, device deficiencies were separately reported from adverse events (see adverse events definition in "Safety Endpoints" on page 2).

**Table 27** is a summary of device deficiencies reported in the INGEVITY study, the SAMURAI study, and the two studies combined. Data are presented as the "number of leads with deficiencies/total number of leads implanted and attempted (% of total)." The rate of occurrence of device deficiencies across both studies was 6.4%. Some examples of device deficiencies include poor visibility of suture sleeve, inability to place the lead, and difficulty with helix extension/retraction. The most common device deficiency observed was difficulty with helix extension/retraction, 3.9% for the INGEVITY study, 6.8% for the SAMURAI study, and 4.8% across both studies.

Some of these helix extension/retraction device deficiencies resulted in lead conductor coil breaks, which were consistent with acute overload and not flex fatigue fracture. The rate of occurrence of lead conductor coil breaks was 1.6% for the INGEVITY study, 3.3% for the SAMURAI study, and 2.1% across both studies. In each case of conductor coil break, inadequate functionality of the lead was identified prior to pocket closure and the lead was removed from service. The leads were subsequently determined to have broken coils based on return product analysis. Implant of a lead with a broken coil during the study was prevented by physician attention to two procedural indicators: a) inability to extend or retract the helix per labeling instructions and/or b) unacceptable electrical measurements as determined by testing per labeling, which includes tests using the pacing system analyzer (PSA) and pulse generator.

Analysis of study data did not show an elevated safety risk of death, adverse events, serious adverse events, or complications for subjects with a helix extension/retraction device deficiency or a lead conductor coil break when compared to those who did not experience a helix extension/retraction device deficiency or lead conductor coil break.

To mitigate the extension/retraction device deficiencies, manufacturing improvements were made and the instructions for use were clarified.

**Table 27: Summary of Device Deficiencies for the INGEVITY study and the SAMURAI study**

| Device Deficiency | Leads Included | INGEVITY | SAMURAI | Total of both |
|---|---|---|---|---|
| All Reported | All | 98/1656 (5.9%) | 54/705 (7.7%) | 152/2361 (6.4%) |
| - Active Fixation | Active Fixation | 91/1322 (6.9%) | 54/601 (9.0%) | 145/1923 (7.5%) |
| - Passive Fixation | Passive Fixation | 7/334 (2.1%) | 0/104 (0.0%) | 7/438 (1.6%) |
| Helix Extension/ Retraction | Active Fixation | 52/1322 (3.9%) | 41/601 (6.8%) | 93/1923 (4.8%) |
| - Right Atrium | RA Active Fixation | 36/475 (7.6%) | 23/299 (7.7%) | 59/774 (7.6%) |
| - Right Ventricle | RV Active Fixation | 16/847 (1.9%) | 18/302 (6.0%) | 34/1149 (3.0%) |
| Coil Breaks* | Active Fixation | 21/1322 (1.6%) | 20/601 (3.3%) | 41/1923 (2.1%) |
| - Right Atrium | RA Active Fixation | 14/475 (2.9%) | 11/299 (3.7%) | 25/774 (3.2%) |
| - Right Ventricle | RV Active Fixation | 7/847 (0.8%) | 9/302 (3.0%) | 16/1149 (1.4%) |

*Coil Breaks are a subset of Helix Extension/Retraction device deficiencies. Note: All implanted and attempted leads are included.

**Deaths that occurred in the PMA clinical study – INGEVITY**

A total of 93 deaths (8.8% of enrolled subjects) were reported for this study. Classification of deaths by the independent Clinical Events Committee (CEC) is provided in **Table 28**. The four "Unclassified" deaths are pending classification, upon review of further source information.

**Table 28: Study Deaths** *(N = 1060 Enrolled Subjects)*

| | | Lead-Related Number (%) of Patients | |
|---|---|---|---|
| **CEC Adjudicated Primary Organ Cause** | **Number (%) of Patients** | **Yes** | **Unknown** |
| Non Cardiac | 46 (4.3%) | 0 (0.0%) | 0 (0.0%) |
| Cardiac: Pump Failure | 6 (0.6%) | 0 (0.0%) | 0 (0.0%) |
| Cardiac: Arrhythmic | 1 (0.1%) | 0 (0.0%) | 0 (0.0%) |
| Cardiac: Unknown | 1 (0.1%) | 0 (0.0%) | 0 (0.0%) |
| Cardiac: Ischemic | 1 (0.1%) | 0 (0.0%) | 0 (0.0%) |
| Cardiac: Other Cardiac | 1 (0.1%) | 0 (0.0%) | 1 (0.1%) |
| Unknown | 33 (3.1%) | 0 (0.0%) | 7 (0.7%) |
| Unclassified | 4 (0.4%) | Not applicable | Not applicable |
| **Total** | **93 (8.8%)** | **0 (0.0%)** | **8 (0.8%)** |

As shown in **Table 28** above, the CEC did not attribute any deaths as related to the INGEVITY lead. Due to insufficient source information on some deaths, the CEC was unable to classify the relationship of the death to the INGEVITY lead in seven of the 33 deaths where the primary organ cause was unknown. Additionally, there was one death due to other cardiac reasons for which the CEC was unable to classify the relationship of the death to the INGEVITY lead.

2. Effectiveness Results

The analysis of effectiveness was based on evaluation of key effectiveness outcomes (Effectiveness Endpoint 1, 2 and 3) at the 3-month time point as presented in **Tables 29** to **32**. There were 1599 leads eligible for endpoint analysis; exact number of leads for each endpoint are described below.

All three effectiveness endpoints were met and are described in detail later in this section.

*EFFECTIVENESS ENDPOINT 1 – PACING THRESHOLD AT 0.5 MS PULSE WIDTH*

The analysis of Effectiveness Endpoint 1 was based on 1482 leads that had bipolar pacing threshold measurements at a 0.5 ms pulse width collected at 3 months post-implant.

The mean pacing threshold for a total of 1482 threshold measurements collected at the 3-month follow-up was 0.67 V with an upper one-sided 95% confidence limit of 0.69 V, resulting in a p-value < 0.001 (see **Table 29**). A total of 98.5% of threshold measurements were at or below the performance goal value of 1.5 V. The results were further analyzed by lead cohort (**Table 29**).

**Table 29: Effectiveness Endpoint 1 Results by Lead Cohort – Pacing Threshold at 0.5 ms Pulse Width**

| Group | Leads | Mean | Standard Deviation | Upper One-sided 95% Confidence Limit | P-value (Perf. Goal = 1.5 V) |
|---|---|---|---|---|---|
| **All Leads** | **1482** | **0.67** | **0.33** | **0.69** | **< 0.001** |
| - Lead Cohort 1: RV Active Fixation | 782 | 0.68 | 0.33 | 0.69 | < 0.001 |
| - Lead Cohort 2: RA Active Fixation | 394 | 0.75 | 0.39 | 0.78 | < 0.001 |
| - Lead Cohort 3: RA/RV Passive Fixation | 306 | 0.57 | 0.19 | 0.59 | < 0.001 |

Since for all cases the mean pacing threshold obtained at 3 months post-implant was significantly lower than the performance goal, the data from analysis of all leads, and from analyses of lead fixation type and chamber, support the effectiveness of the INGEVITY lead at 3 months post-implant.

*EFFECTIVENESS ENDPOINT 2 – SENSED AMPLITUDE IN THE RA AND RV*

The analysis of Effectiveness Endpoint 2 was based on 521 right atrial leads and 914 right ventricular leads that had sensed amplitude measurements collected at 3 months post-implant. Analysis was performed separately for each heart chamber.

A total of 521 atrial sensed amplitude measurements (409 active fixation and 112 passive fixation) were taken at the 3-month follow-up visit and included in the endpoint analysis. The mean sensed amplitude in the right atrium was 4.8 mV with a lower one-sided 95% confidence limit of 4.6 mV, resulting in a p-value < 0.001 (see

**Table** 30). A total of 914 ventricular sensed amplitude measurements (738 active fixation and 176 passive fixation) were taken at the 3-month follow-up visit and included in the endpoint analysis. The mean sensed amplitude in the right ventricle was 16.5 mV with a lower one-sided 95% confidence limit of 16.2 mV, resulting in a p-value < 0.001 (see **Table 31**). A total of 91.6% of measurements in the atrium and 96.4% of measurements in the ventricle were at or above the performance goals of 1.5 mV and 5.0 mV, respectively.

**Table 30: Effectiveness Endpoint 2 Results by Lead Cohort – Sensed Amplitudes in the Right Atrium**

| Group | Leads | Mean | Standard Deviation | Lower 1-sided 95% Confidence Limit | P-value (Perf Goal = 1.5 mV) |
|---|---|---|---|---|---|
| **All Right Atrial Leads** | **521** | **4.8** | **2.6** | **4.6** | **< 0.001** |
| - Lead Cohort 2: RA Active Fixation | 409 | 4.8 | 2.7 | 4.6 | < 0.001 |
| - Lead Cohort 3: RA Passive Fixation | 112 | 4.7 | 2.5 | 4.3 | < 0.001 |

**Table 31: Effectiveness Endpoint 2 Results by Lead Cohort – Sensed Amplitudes in the Right Ventricle**

| Group | Leads | Mean | Standard Deviation | Lower 1-sided 95% Confidence Limit | P-value (Perf. Goal = 5 mV) |
|---|---|---|---|---|---|
| **All Right Venricular Leads** | **914** | **16.5** | **6.5** | **16.2** | **< 0.001** |
| - Lead Cohort 1: RV Active Fixation | 738 | 16.7 | 6.5 | 16.3 | < 0.001 |
| - Lead Cohort 3: RV Passive Fixation | 176 | 16.0 | 6.5 | 15.2 | < 0.001 |

Since the mean sensed amplitude obtained in both the right atrium and the right ventricle at 3 months post-implant was significantly greater than the respective performance goals, these data also support the effectiveness of the INGEVITY lead at 3 months post-implant.

*EFFECTIVENESS ENDPOINT 3 – PACING IMPEDANCE*

The analysis of Effectiveness Endpoint 3 was based on 1526 leads that had pacing impedance measurements collected at 3 months post-implant. The mean pacing impedance was 773 Ω with a confidence interval of 766 to 779 Ω, between the performance goals of 300 and 1300 Ω, resulting in a p-value < 0.001 (see **Table 32**). A total of 98.6% measurements were observed to be between the performance goals of 300 and 1300 Ω.

The results were further analyzed by lead cohort (**Table 32**).

**Table 32: Effectiveness Endpoint 3 Results by Lead Cohort – Pacing Impedance**

| Group | Leads | Mean | Standard Deviation | 90% Confidence Interval | P-value (Perf. Goals = 300, 1300 ohms) |
|---|---|---|---|---|---|
| **All Leads** | **1526** | **773** | **155** | **(766, 779)** | **< 0.001** |
| - Lead Cohort 1: RV Active Fixation | 795 | 824 | 158 | (815, 834) | < 0.001 |
| - Lead Cohort 2: RA Active Fixation | 420 | 711 | 139 | (700, 722) | < 0.001 |
| - Lead Cohort 3: RA/RV Passive Fixation | 311 | 724 | 116 | (713, 734) | < 0.001 |

The overall mean pacing impedance obtained at 3 months post-implant for all groups of leads was within the performance goal range, and supports the effectiveness of the INGEVITY lead at 3 months post-implant.

3. Subgroup Analyses

The following preoperative and device characteristics were evaluated for potential association with outcomes: lead fixation (active versus passive), lead chamber (RA versus RV), geography (US versus international), age (<65 versus ≥65), sex and pulse generator (pacemaker versus CRT-P). There were no significant differences observed between subgroups for any safety endpoint. Some significant differences were observed between subgroups for effectiveness endpoints; however, in every case in which subgroups differed each subgroup individually passed the endpoints.

4. INGEVITY Clinical Study Conclusion

The safety profile of the INGEVITY leads was assessed using the lead-related complications through the entire study to date. All three safety endpoints were met. The effectiveness profile of the INGEVITY leads was assessed by evaluating pacing thresholds, sensed amplitude, and pacing impedance via three endpoints and in each endpoint the performance goal was met. Therefore, all effectiveness endpoints were met. This indicates that the overall safety and effectiveness profile of the implanted leads is similar to approved devices.

### E. Financial Disclosure – INGEVITY

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The INGEVITY clinical study included 78 Principal Investigators and 183 SubInvestigators. Among the investigators involved in the study, 258 have, by way of a signed Certification of Investigator Financial Interest Form, verified that they have no applicable financial arrangement with Boston Scientific defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

The INGEVITY clinical study included three Investigators that have disclosable financial arrangements with INGEVITY disclosed under 21 CFR 54.2, not affecting the outcome of the INGEVITY clinical study. The nature of these disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) is described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 3
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

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

## XII. SUMMARY OF PRIMARY CLINICAL STUDY FOR THE MRI SYSTEM

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of implantation the ImageReady™ MR Conditional Pacing System (ImageReady System) when subjects receive MRI scans up to 4W/kg Specific Absorption Rate (SAR) without positioning restrictions (MRI scans may occur anywhere on the body) in the US and internationally under IDE G120076. Data from this clinical study were the basis for the PMA approval decision, along with data from the INGEVITY study under IDE G110227 (see Section XI for details). A summary of the clinical study is presented below.

### A. Study Design - SAMURAI

Patients were treated between February 14, 2013 and July 25, 2014. Treatment was defined as implanted or attempted with at least one component of the ImageReady

System. The database for this PMA reflected data collected through February 17, 2016 and included 363 patients. There were 41 investigational sites.

The SAMURAI Clinical Study is a prospective, open-label, two-group randomized clinical study with parallel groups conducted at multiple centers globally. Patients were randomized 2:1 to receive a protocol-required MRI scan (MRI Group) or not receive a scan (Control Group).

The study used a Clinical Events Committee (CEC) as a group of independent evaluators to adjudicate safety endpoint events and mortality. A Data Monitoring Committee reviews accumulating safety data to monitor the incidence of adverse events, deaths and other trends that would warrant modification or termination of the study. An Image Artifact Core Lab assessed MR scan image artifact in the torso region in a subset of the MR scan images. The core lab includes leading experts in Radiology and MR imaging.

The study has been conducted through the MRI + 1 month (3 months post-implant) follow-up endpoints to collect data to support US pre-market approval of the ImageReady System. Data continues to be collected via annual follow-ups at 1 through 5 years in support of post-market approval requirements.

Data was required to be collected from subjects upon enrollment into the study, at implant, and pre-discharge. The randomization order for subjects was available within their pre-discharge follow up eCRF. Subjects randomized to the MRI Group had an MR scan (including scans of the chest region), while those in the Control Group had a data collection follow up at 6-9 weeks post-implant, or at least 6 weeks after any required surgical interventions to the ImageReady System (labeled as MRI Visit or Control Group Visit). Subsequently, there was a clinic follow-up at MRI Visit + 1 Week, and another clinic follow-up at MRI Visit + 1 Month.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the SAMURAI study was limited to patients who met the all of the following inclusion criteria:

- All implanted devices must be the initial (de novo) pacing system implants for the subject and consist only of ImageReady MR Conditional Pacing System pacemaker and lead(s)
- Have a Class I or II indication for implantation of a single or dual chamber pacemaker according to the American College of Cardiology (ACC)/American Heart Association (AHA)/Hearth Rhythm Society (HRS)[12], or European Society of Cardiology (ESC)[13], as appropriate per geography

[12] Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002

- Willing and capable of undergoing an MR Scan without intravenous sedation. (Oral sedation may be used, if necessary, based on medical discretion)
- Willing and capable of providing informed consent (which can include the use of a legally authorized representative (LAR) for documentation of informed consent) and participating in all testing/visits associated with this clinical study at an approved clinical study center and at the intervals defined by this protocol
- Age 18 or above, or of legal age to give informed consent specific to state and national law

Patients were not permitted to enroll in the SAMURAI study if they met any of the following exclusion criteria:

- Has or has had any pacing or ICD system implants
- Has any MR Unsafe implants or devices with an unknown MR status, including MR Unsafe sternal wires, neurostimulator, biostimulator, metals or alloys, per labeling of each implant
- Has any MR Conditional implants or devices that impact the ability to conduct this protocol
- Needs or will need another MR scan, other than that required by the SAMURAI Study, within 14 weeks of system implant
- Known or suspected sensitivity to dexamethasone acetate (DXA)
- Mechanical tricuspid heart valve
- Enrolled in any other concurrent study, with the exception of local mandatory governmental registries and observational studies/registries that are not in conflict and do not affect the following:
    - Schedule of procedures for the SAMURAI Study (i.e., should not cause additional or missed visits)
    - SAMURAI Study outcome (i.e., involve medications that could affect pacing thresholds)
    - Conduct of the SAMURAI Study per GCP/ ISO 14155:2011/ 21 CFR 812, local regulations
- Documented permanent or persistent AF[14] where the physician intends to implant a dual chamber pulse generator (single chamber VVIR pulse generators are acceptable)
- Currently on the active heart transplant list

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Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) Developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons Circulation 2008;117: e350-e408.

[13] Vardas PE, Auricchio A, Blanc J, et al. Guidelines for cardiac pacing and cardiac resynchronization therapy: The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. Europace 2007; 9: 959-998.

[14] Calkins H, et al. HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. Heart Rhythm 4:816-861, 2007

- Documented life expectancy of less than 12 months
- Women of childbearing potential who are or might be pregnant at the time of study enrollment or ImageReady System implant (method of assessment up to physician's discretion)
- Currently requiring dialysis

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at pre-discharge (3-72 hours post-implant), MRI visit at 6-9 weeks post-implant, MRI visit + 1 week, MRI visit + 1 month, and 12, 24, 36, 48 and 60 months postoperatively. Preoperative and postoperative evaluations and objective parameters measured are listed in the following table. Adverse events and complications were required per the protocol to be reported at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

**Table 33: Data Collection Schedule**

| Procedure/ Assessment | Enroll-ment | Implant | Pre-Discharge | MRI Visit | MRI Visit + 1 Week | MRI Visit + 1 Month | 1, 2, 3, 4, 5 Yrs | Add'l Visits | Medically necessary MRI |
|---|---|---|---|---|---|---|---|---|---|
| **Timeframe** *, **, Δ: See below table | ≤ 30 d prior to Implant | Implant | 3-72 h* Clinic Visit | 6-9 wks (42-63 d)* / Δ Procedure & Clinic Visit | 7 ± 3 d** Clinic Visit | 30 ± 7 d** Clinic Visit | 1 yr: 365±45 d* 2 yr: 730±90 d* 3 yr: 1095±90 d* 4 yr: 1461±90 d* 5 yr: 1826±90 d* Clinic Visit | Not specified | Not specified |
| ICF Process | X | -- | -- | -- | -- | -- | -- | -- | -- |
| Subject demographics | X | -- | -- | -- | -- | -- | -- | -- | -- |
| Physical assessment | X | -- | -- | -- | -- | -- | -- | -- | -- |
| Medical history | X | -- | -- | -- | -- | -- | -- | -- | -- |
| PSA measurements (pacing threshold(s) @ 0.5ms) | -- | X | -- | -- | -- | -- | -- | -- | -- |
| PA and lateral CXR and/or fluoro image of lead distal tip fixation | -- | X | | -- | -- | -- | -- | -- | -- |
| Implant Questionnaire | -- | X | -- | -- | -- | -- | -- | -- | -- |
| Post MR Scan Questionnaire | -- | -- | -- | X MRI group | -- | -- | -- | -- | O |
| Cardiovascular Medications (Class I/ III only), including updates and changes | X | X | X | X | X | X | X | O | O |
| IPG lead measurements (pacing threshold(s) @ 0.5ms thru MRI Visit + 1 Month) | -- | X | X | X | X | X | X | O | O |

| Procedure/ Assessment | Enroll-ment | Implant | Pre-Discharge | MRI Visit | MRI Visit + 1 Week | MRI Visit + 1 Month | 1, 2, 3, 4, 5 Yrs | Add'l Visits | Medically necessary MRI |
|---|---|---|---|---|---|---|---|---|---|
| ECG documenting LOC | -- | X | X | X | X | X | -- | O | -- |
| MR Scan Conditions of Use | -- | -- | -- | X | -- | -- | -- | -- | X |
| DICOM file from MR scanner | -- | -- | -- | X MRI group Include images | -- | -- | -- | -- | O Do not include images |
| Adverse Events | X | X | X | X | X | X | X | X | X |
| Protocol Deviations | X | X | X | X | X | X | X | X | -- |

**Legend: X** = Required; **--** = Not required/ Not applicable; **O** = Optional; h = hours; d = days; wk(s) = week(s); yr = year; ECG = Electrocardiogram;
**Abbreviations: LOC** = Loss of Capture; **IPG** = Implantable Pulse Generator; **PSA** = Pacing System Analyzer; **PA** = Posterior-Anterior; **CXR** = Chest X=ray; **AE** = Adverse Event; **Add'l** = Additional; **ICF** = Informed Consent Form
*****Clock starts after end of Implant procedure, day of implant is day 0 and hour 0 is pocket closure
**Timing based on MRI Visit
$^{\Delta}$ Must be at least 6 weeks after any required surgical interventions to the ImageReady System

*FOLLOW-UP EXPERIENCE*

The follow-up visit compliance for all succesfully implanted and randomized subjects is presented in

**Table** 34.

**Table 34: SAMURAI Study Follow up Compliance**

| | | | | | Randomized Group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | All Subjects (N=363) | | | MRI Group (N=229) | | | Control Group (N=118) | | |
| Visit | Visit Window | Expected No. of Visits | Completed Visits | Visit in Window | Expected No. of Visits | Completed Visits | Visit in Window | Expected No. of Visits | Completed Visits | Visit in Window |
| Implant | Not applicable | 350 | 350 (100.0%) | N/A | 229 | 229 (100.0%) | N/A | 118 | 118 (100.0%) | N/A |
| Pre-Discharge | 3 – 72 hours post-implant | 350 | 350 (100.0%) | 347 (99.1%) | 229 | 229 (100.0%) | 227 (99.1%) | 118 | 118 (100.0%) | 117 (99.2%) |
| MRI Visit (includes Control Group Visit) | 6-9 weeks post-implant | 345 | 335 (97.1%) | 300 (87.0%) | 227 | 220 (96.9%) | 195 (85.9%) | 118 | 115 (97.5%) | 105 (89.0%) |

| | | | | | Randomized Group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | All Subjects (N=363) | | | MRI Group (N=229) | | | Control Group (N=118) | | |
| Visit | Visit Window | Expected No. of Visits | Completed Visits | Visit in Window | Expected No. of Visits | Completed Visits | Visit in Window | Expected No. of Visits | Completed Visits | Visit in Window |
| MRI + 1 Week | 7 ± 3 days post-MRI Visit | 344 | 331 (96.2%) | 317 (92.2%) | 226 | 218 (96.5%) | 208 (92.0%) | 118 | 112 (94.9%) | 109 (92.4%) |
| MRI + 1 Month | 30 ± 7 days post-MRI Visit | 341 | 330 (96.8%) | 292 (85.6%) | 224 | 217 (96.9%) | 195 (87.1%) | 117 | 113 (96.6%) | 97 (82.9%) |

3. Clinical Endpoints

*SAFETY ENDPOINTS*

With regard to safety, the following endpoints were evaluated for the ImageReady™ MR Conditional Pacing System, to satisfy US regulatory requirements.

- Primary Safety Endpoint: MR Scan-related ImageReady System Complication-Free Rate from MR Scan through the MRI Visit + 1 Month Follow-up. This endpoint will be analyzed for subjects randomized to the MRI group only. For the purpose of this endpoint, a complication will be defined as those detectable adverse events that may only be resolved by invasive intervention or that cause significant loss of device function. Significant loss of device function is defined as any pacemaker that reverts to Safety Core, or any pacemaker rendered unable to deliver pacing. All complications will be adjudicated by an external Clinical Events Committee for relation to the MR scan. MR scan-related complications will be further adjudicated for their relation to the ImageReady System. Complications that are determined to be associated with both MR scan and the ImageReady system will be considered MR scan-related complications and count against this endpoint.

- Secondary Safety Endpoint: System-related Complication-Free Rate from Implant through 3 months post-implant. This endpoint will be analyzed for the entire study cohort. Adverse event data will be collected for the purpose of this endpoint at Implant, Pre-Discharge, MRI Visit, MRI Visit + 1 Week and MRI Visit + 1 Month, as well as any additional follow-ups in this time period. All complications will be adjudicated by an external Clinical Events Committee for relation to the system. Any adverse events that occur within 91 days of initial ImageReady System implant and adjudicated as a system-related complication will count against this endpoint.

*EFFECTIVENESS ENDPOINTS*

With regard to effectiveness, the following endpoints were evaluated for the ImageReady System, to satisfy US regulatory requirements.

- Primary Effectiveness Endpoint 1: Change in Pacing Threshold (at 0.5 ms pulse width) pre- and 1-Month post-MR Scan or Control Group Visit compared between the MRI and Control Groups. This will be analyzed at the MRI Visit + 1 Month Follow-up.
- Primary Effectiveness Endpoint 2: Change in Sensed Amplitude pre- and 1-Month post-MR Scan or Control Group Visit compared between the MRI and Control Groups. This will be analyzed at the MRI Visit + 1 Month Follow-up.

*SUCCESS/FAILURE CRITERIA*

With regard to success/failure criteria, the study was required to pass all primary and secondary endpoints.

## B. Accountability of PMA Cohort

At the time of database lock, a total of 363 subjects were enrolled at 41 centers, including 254 (70%) enrollments at 29 sites in the United States and 109 (30%) enrollments at 12 sites in the international geography, as described in **Table** 35.

**Table 35: SAMURAI Enrollments per country**

| Country | Number of Centers with Enrollments | Number of Enrollments |
|---|---|---|
| United States | 29 (70.7) | 254 (70.0) |
| Israel | 4 (9.8) | 36 (9.9) |
| Malaysia | 2 (4.9) | 32 (8.8) |
| Singapore | 3 (7.3) | 21 (5.8) |
| Hong Kong | 1 (2.4) | 10 (2.8) |
| Canada | 1 (2.4) | 8 (2.2) |
| Australia | 1 (2.4) | 2 (0.6) |
| **Total** | **41** | **363** |

Of the 363 enrolled subjects, 348 were successfully implanted with the ImageReady™ MR Conditional Pacing System. 347 subjects were randomized. Among these 347 randomized subjects, 245 (71%) were from the US and 102 (29%) were from outside the US. The study flowchart (Figure 5) accounts for subject withdrawal due to death or exits and denotes missing follow-up visit data. A subject could miss a follow-up visit, and still contribute data at a subsequent follow-up visit.

94% (341) of patients were under follow-up and therefore available for analysis at the MRI+1-month visit.

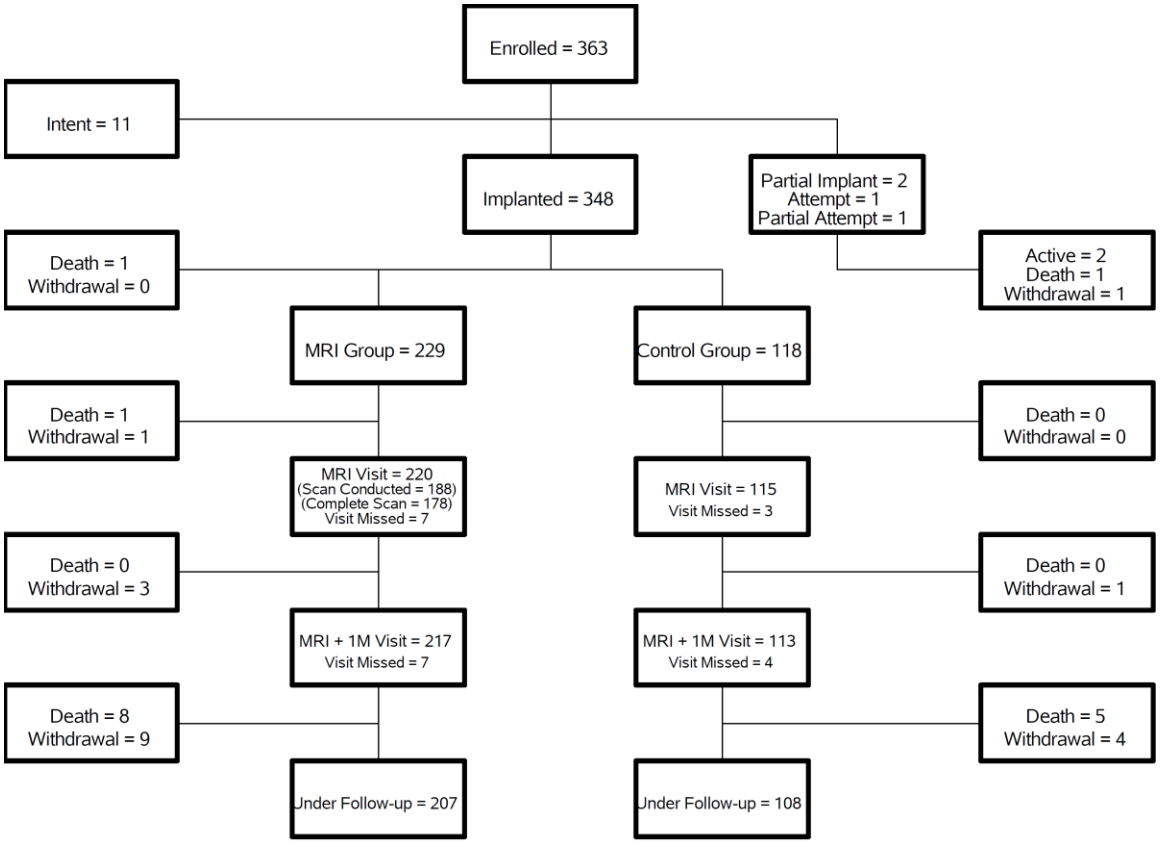


**Figure 10: SAMURAI Subjects disposition**

The first subject enrollment occurred on February 14, 2013 and enrollment was completed on July 14, 2014. The last MRI + 1 month visit was performed on October 28, 2014. Results include any visit or event that occurred on or before February 17, 2016. This dataset represents the data submitted in support of the PMA; however, subject follow-up continued beyond this date, with subjects and leads followed for a median of 23 months.

*DATA CONTRIBUTING TO ENDPOINTS*

There were 363 patients enrolled in the study. Not all patients contributed to study endpoints. **Table 36** summarizes the data contributing to each of the endpoints.

**Table 36: Datasets included in Endpoints**

| | | Complete Datasets Included in Endpoint Analyses N (%) | |
|---|---|---|---|
| **Endpoint** | **Description** | **MRI Subjects N=229** | **Control Group Subjects N=118** |
| Primary Safety Endpoint | MR Scan-related Complication-Free Rate (CFR) Analyzed at MRI Visit + 1 Month (MRI Group only) | 180 (78.6%) | N/A |
| Secondary Safety Endpoint | System-related Complication-Free Rate (CFR) from Implant through 3 Months Post-Implant | 325 (92.6%) | |
| Primary Effectiveness Endpoint 1 ITT | Pacing Threshold (at 0.5 ms pulse width) comparison pre- and 1 Month post-MR Scan or Control Group Visit and between the MRI and Control Groups | 203 (88.6%) | 101 (85.6%) |
| Primary Effectiveness Endpoint 1 PP | Pacing Threshold (at 0.5 ms pulse width) comparison pre- and 1 Month post-MR Scan or Control Group Visit and between the MRI and Control Groups | 167 (72.9%) | 96 (81.4%) |
| Primary Effectiveness Endpoint 2 ITT (RA) | Sensed Amplitude comparison pre- and 1 Month post-MR Scan or Control Group Visit and between MRI and Control Groups. | 167 (81.5%) | 83 (76.1%) |
| Primary Effectiveness Endpoint 2 PP (RA) | Sensed Amplitude comparison pre- and 1 Month post-MR Scan or Control Group Visit and between MRI and Control Groups. | 135 (65.9%) | 78 (71.6%) |
| Primary Effectiveness Endpoint 2 ITT (RV) | Sensed Amplitude comparison pre- and 1 Month post-MR Scan or Control Group Visit and between MRI and Control Groups. | 181 (80.1%) | 96 (81.4%) |
| Primary Effectiveness Endpoint 2 PP (RV) | Sensed Amplitude comparison pre- and 1 Month post-MR Scan or Control Group Visit and between MRI and Control Groups. | 152 (67.3%) | 91 (77.1%) |

Statistical analyses were performed and determined that the missing/excluded data were highly unlikely to affect the conclusions from the study.

## C. Study Population Demographics and Baseline Parameters

Although the study was performed globally, the demographics of the study population are typical for a pacemaker MRI system study performed in the US.

Baseline characteristics, including subject demographics and the primary indication for succesfully randomized subjects, are summarized in

**Table** 37 and **Table 38**.

**Table 37: SAMURAI Subject Demographics**

| | | | Randomized Group | | |
|---|---|---|---|---|---|
| **Characteristic** | **Measurement** | **All Subjects (N=363)** | **MRI Group (N=229)** | **Control Group (N=118)** | **p-value** |
| Age at Implant (years) | Mean +/- SD (Median)<br>Range | 69.4 +/- 12.8 (71.0)<br>25.0-90.0 | 69.0 +/- 13.0 (71.0)<br>29.0-90.0 | 70.4 +/- 11.9 (72.5)<br>25.0-90.0 | 0.34 |
| Gender [N (%)] | Female | 169 (46.6) | 102 (44.5) | 63 (53.4) | 0.12 |
| | Male | 194 (53.4) | 127 (55.5) | 55 (46.6) | |
| Race [N (%)] | Caucasian | 266 (74.5) | 170 (75.6) | 85 (72.6) | 0.56 |
| | Asian | 71 (19.9) | 43 (19.1) | 24 (20.5) | |
| | Black, of African heritage | 17 (4.8) | 9 (4.0) | 8 (6.8) | |
| | Other | 2 (0.6) | 2 (0.9) | 0 (0.0) | |
| | Not disclosed | 1 (0.3) | 1 (0.4) | 0 (0.0) | |
| Body Mass Index ($kg/m^2$) | Mean +/- SD (Median)<br>Range | 28.4 +/- 5.6 (27.2)<br>16.4-52.3 | 27.9 +/- 5.2 (27.1)<br>16.4-44.1 | 29.3 +/- 6.0 (27.6)<br>18.9-47.6 | 0.030 |
| Body Surface Area ($m^2$)) | Mean +/- SD (Median)<br>Range | 1.9 +/- 0.3 (1.9 )<br>1.2-2.8 | 1.9 +/- 0.3 (1.9 )<br>1.2-2.7 | 1.9 +/- 0.3 (1.9 )<br>1.2-2.5 | 0.95 |
| Atrial Arrhythmia History* [N (%)] | Paroxysmal Atrial Fibrillation | 112 (30.9) | 73 (31.9) | 37 (31.4) | 0.92 |
| | Atrial Tachycardia/Flutter | 52 (14.3) | 34 (14.8) | 14 (11.9) | 0.45 |
| | Permanent Atrial Fibrillation | 20 (5.5) | 15 (6.6) | 3 (2.5) | 0.11 |
| | Persistent Atrial Fibrillation | 18 (5.0) | 12 (5.2) | 5 (4.2) | 0.68 |
| | Other Atrial Arrhythmia | 22 (6.1) | 11 (4.8) | 10 (8.5) | 0.17 |
| | None | 182 (50.1) | 110 (48.0) | 62 (52.5) | 0.43 |
| Brady Arrhythmia History* [N (%)] | Sinus Node Dysfunction | 161 (44.4) | 106 (46.3) | 50 (42.4) | 0.49 |
| | Sinus Bradycardia | 153 (42.1) | 101 (44.1) | 45 (38.1) | 0.29 |
| | 2nd Degree AV Block - Intermittent | 40 (11.0) | 18 (7.9) | 19 (16.1) | 0.018 |
| | 3rd Degree AV Block - Intermittent | 42 (11.6) | 27 (11.8) | 10 (8.5) | 0.34 |

| | | | Randomized Group | | |
|---|---|---|---|---|---|
| **Characteristic** | **Measurement** | **All Subjects (N=363)** | **MRI Group (N=229)** | **Control Group (N=118)** | **p-value** |
| | 1st Degree AV Block | 34 (9.4) | 25 (10.9) | 7 (5.9) | 0.13 |
| | 3rd Degree AV Block - Permanent | 31 (8.5) | 20 (8.7) | 9 (7.6) | 0.72 |
| | Chronotropic Incompetence | 28 (7.7) | 17 (7.4) | 11 (9.3) | 0.54 |
| | Sinus Arrest | 25 (6.9) | 14 (6.1) | 9 (7.6) | 0.59 |
| | 2nd Degree AV Block - Permanent | 21 (5.8) | 12 (5.2) | 7 (5.9) | 0.79 |
| | Other | 87 (24.0) | 57 (24.9) | 26 (22.0) | 0.55 |
| Associated Diseases and Risk Factors* [N (%)] | Hypertension | 262 (72.2) | 162 (70.7) | 89 (75.4) | 0.36 |
| | Diabetes | 81 (22.3) | 52 (22.7) | 27 (22.9) | 0.97 |
| | Coronary Artery Disease | 73 (20.1) | 44 (19.2) | 27 (22.9) | 0.42 |
| | Renal Disease | 41 (11.3) | 23 (10.0) | 14 (11.9) | 0.60 |
| | Cerebrovascular Disease | 35 (9.6) | 25 (10.9) | 8 (6.8) | 0.21 |
| | Chronic Pulmonary Disease | 26 (7.2) | 22 (9.6) | 3 (2.5) | 0.016 |
| | Peripheral Vascular Disease | 20 (5.5) | 15 (6.6) | 5 (4.2) | 0.38 |
| | Hypertrophic Cardiomyopathy | 8 (2.2) | 4 (1.7) | 4 (3.4) | 0.33 |
| | Ischemic Cardiomyopathy | 7 (1.9) | 4 (1.7) | 2 (1.7) | 0.97 |
| | Idiopathic Conduction System Disease | 5 (1.4) | 2 (0.9) | 3 (2.5) | 0.22 |
| | Idiopathic Cardiomyopathy | 6 (1.7) | 1 (0.4) | 5 (4.2) | 0.010 |
| | Congenital Heart Disease | 3 (0.8) | 2 (0.9) | 1 (0.8) | 0.98 |
| | Valvular Cardiomyopathy | 3 (0.8) | 1 (0.4) | 1 (0.8) | 0.63 |
| | Other | 151 (41.6) | 100 (43.7) | 44 (37.3) | 0.25 |

| | | | Randomized Group | | |
|---|---|---|---|---|---|
| **Characteristic** | **Measurement** | **All Subjects (N=363)** | **MRI Group (N=229)** | **Control Group (N=118)** | **p-value** |
| | None | 50 (13.8) | 34 (14.8) | 16 (13.6) | 0.75 |
| * Subjects may contribute to more than one category | | | | | |

**Table 38: Primary Pacemaker Indications** *(N=363 Subjects)*

| | | Randomized Group | |
|---|---|---|---|
| **Indication** | **All Patients (N=363)** | **MRI Group (N=229)** | **Control Group (N=118)** |
| Sinus Node Dysfunction | 154 (42.4) | 100 (43.7) | 49 (41.5) |
| 3rd Degree AV Block | 71 (19.6) | 45 (19.7) | 19 (16.1) |
| 2nd Degree AV Block | 50 (13.8) | 25 (10.9) | 22 (18.6) |
| Other Block (i.e. Chronic Bifascicular Block) | 11 (3.0) | 6 (2.6) | 5 (4.2) |
| Neurocardiogenic Syncope | 6 (1.7) | 4 (1.7) | 2 (1.7) |
| Carotid Sinus Syndrome | 3 (0.8) | 2 (0.9) | 1 (0.8) |
| Other | 68 (18.7) | 47 (20.5) | 20 (16.9) |

## D. Safety and Effectiveness Results – SAMURAI

### 1. Safety Results

The analysis of safety was based on evaluation of:

a) key safety outcomes of Primary Safety Endpoint among 180 patients and Secondary Safety Endpoint among 325 patients eligible for endpoint analysis;
b) adverse events among 351 patients implanted or attempted with at least one component of the ImageReady System; and
c) deaths among 363 enrolled patients.

To be eligible for Primary Safety endpoint analysis the patient must have been randomized to the MRI Group and receive the protocol-required MRI scan. To be eligible for Secondary Safety endpoint analysis the patient must have been implanted or attempted with at least one component of the ImageReady System during the intitial implantation procedure. The available timeframe of the analysis is discussed under each endpoint below. The key safety outcomes for this study are presented below in **Tables 39** and **40**. Adverse events (adverse effects) and deaths are reported in **Tables 41** and **42**.

Both safety endpoints were met and are described in detail later in this section.

*PRIMARY SAFETY ENDPOINT: MR-RELATED COMPLICATIONS*

The analysis of the Primary Safety Endpoint was based on the cohort of 180 patients patients randomized to the MRI Group that received the protocol-required MRI scan. scan. The MR scan-related Complication-free rate (CFR) between the MR Scan and the and the MRI Visit + 1 Month was assessed with a performance goal of 95%.The MR scan MR scan Complication Free Rate was 100% with a 95% one-sided lower confidence confidence interval of 100%. The result is shown in

**Table** 39 and **Figure 11**.

**Table 39: Primary Safety Endpoint Results – MR scan-related Complication-Free Rate between the MR scan and 31 days post-MR scan**

| Group | Subjects at Risk | Subjects with a MR Scan-Related Complication | MRI-Related Complication Free Rate | 95% One-Sided Lower Conf Limit |
|---|---|---|---|---|
| MRI subjects receiving an MR scan | 180 | 0 | 100.0% | 100.0% |

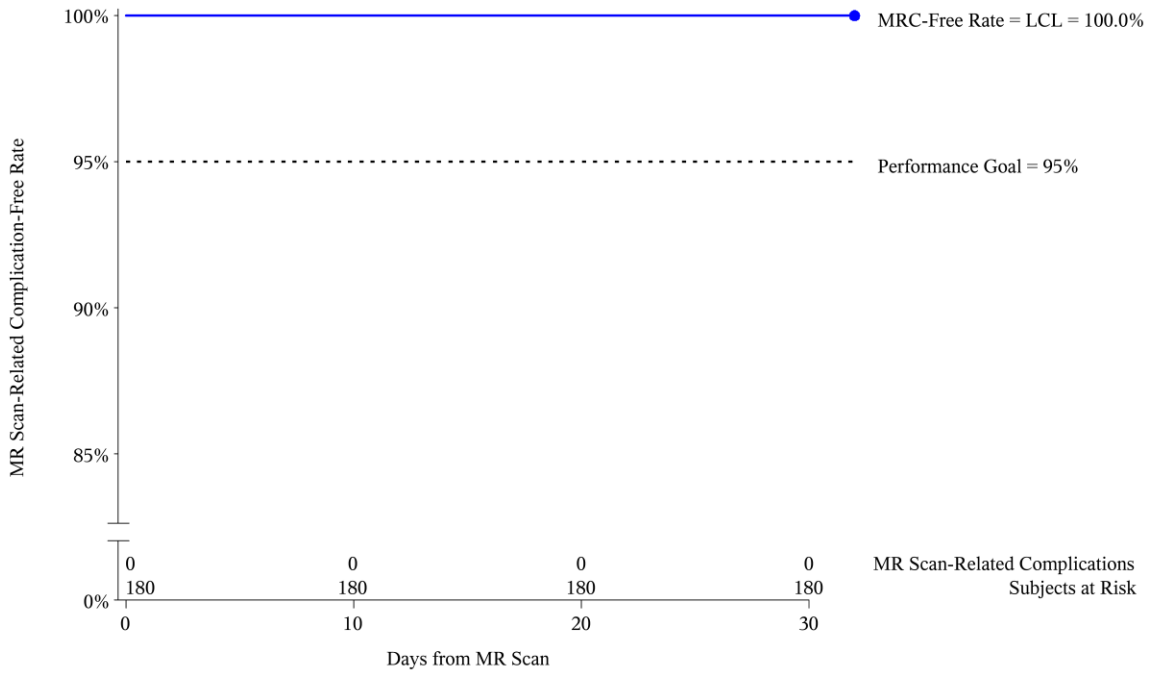


**Figure 11: Safety Endpoint 1 Results – MR Scan-Related Complication-Free Rate from 0 to 3 Months**

*SECONDARY SAFETY ENDPOINT: SYSTEM-RELATED COMPLICATIONS*

The analysis of the Secondary Safety Endpoint was based on the cohort of 325 patients implanted or attempted with at least one component of the ImageReady System during the intitial implantation procedure. The overall safety of the ImageReady™ MR Conditional Pacing System was assessed by evaluating system-related complications that occur from system implant through 3 months post-implant for subjects in both the MRI and Control groups.The ImageReady system-related CFR from implant through 3 months post-implant performance goal was greater than 80%. The system-related complication free rate was 94.5% with a 95% one-sided lower confidence interval of 91.9%. The result is shown in **Table 40** and **Figure 12**.

**Table 40: Secondary Safety Endpoint Results – System-Complication-Free Rate from 0 to 3 Months**

| Group | Subjects at Risk | Subjects with a System-Related Complication | System-Related Complication Free Rate | 95% One-Sided Lower Conf Limit |
|---|---|---|---|---|
| All implant, partial implant and attempt subjects | 325 | 18 | 94.5% | 91.9% |

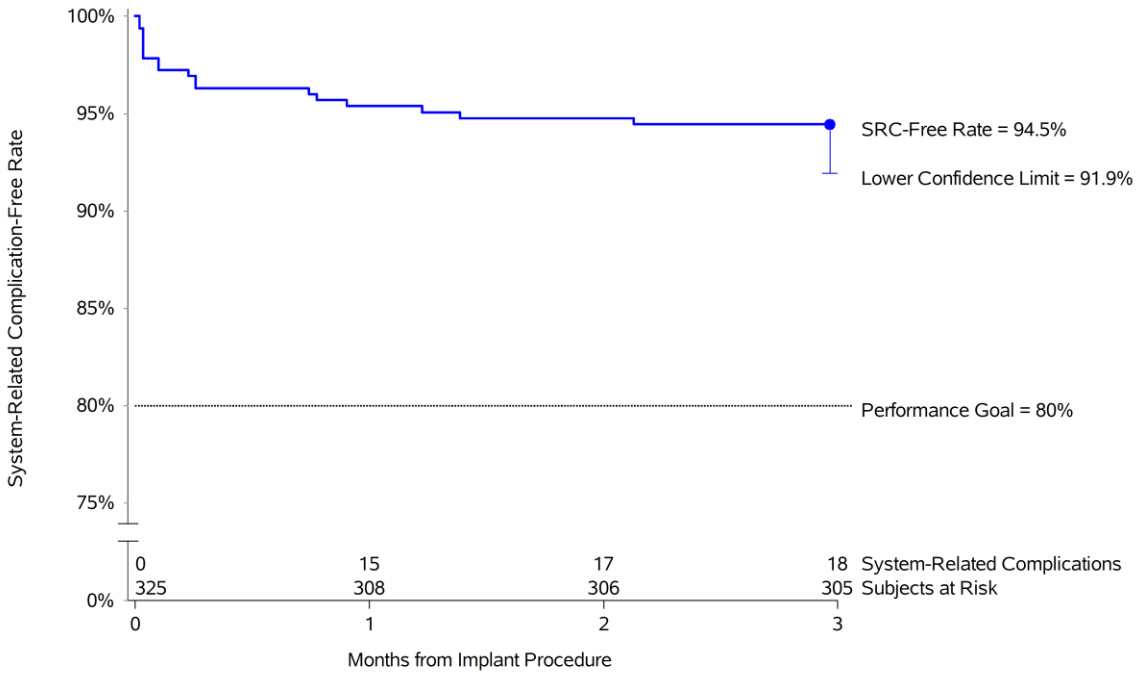


**Figure 12: Secondary Safety Endpoint Results – System-Related Complication-Free Rate from 0 to 3 Months**

**Adverse Events that occurred in the PMA clinical study – SAMURAI**

There have been no reported unanticipated adverse device effects in the study as of February 17, 2016. There were no reported MR-related complications. Of the 351 implanted, partially implanted or attempted subjects, 94.3% were free from adverse events related to the PG, 89.7% were free from adverse events related to the implant procedure; 94.3% and 95.7 were free from adverse events related to the INGEVITY MRI RA and RV leads, respectively.

**Table 41** provides a summary of all Adverse Events reported in the SAMURAI study. See **Section XIII.B. Summary of the Lead-Related Adverse Event Data Collected Across the INGEVITY and SAMURAI Studies** for a summary of adverse events related to the INGEVITY lead.

**Table 41: SAMURAI Study Adverse Events Summary**

| | | | Classification | | | |
|---|---|---|---|---|---|---|
| | Total | | Complication | | Observation | |
| Classification | Events | N (%) | Events | N (%) | Events | N (%) |
| Total (N at risk = 351) | 964 | 275 (78.3%) | 294 | 146 (41.6%) | 664 | 237 (67.5%) |
| PG (N at risk = 351) | 23 | 20 (5.7%) | 1 | 1 (0.3%) | 22 | 19 (5.4%) |
| RA Lead (N at risk = 314) | 18 | 18 (5.7%) | 8 | 8 (2.5%) | 10 | 10 (3.2%) |
| RV Lead (N at risk = 347) | 16 | 15 (4.3%) | 9 | 9 (2.6%) | 7 | 7 (2.0%) |
| Procedure (N at risk = 351) | 46 | 36 (10.3%) | 12 | 11 (3.1%) | 34 | 28 (8.0%) |
| Protocol Testing (N at risk = 351) | 5 | 5 (1.4%) | 0 | 0 (0.0%) | 5 | 5 (1.4%) |
| Cardiovascular - HF (N at risk = 351) | 41 | 29 (8.3%) | 30 | 22 (6.3%) | 11 | 10 (2.8%) |
| Cardiovascular - Non-HF (N at risk = 351) | 325 | 177 (50.4%) | 72 | 61 (17.4%) | 253 | 147 (41.9%) |
| Non-cardiovascular (N at risk = 351) | 450 | 174 (49.6%) | 149 | 77 (21.9%) | 301 | 140 (39.9%) |
| Other (N at risk = 351) | 34 | 23 (6.6%) | 13 | 10 (2.8%) | 21 | 14 (4.0%) |
| Unclassified (N at risk = 351) | 6 | 6 (1.7%) | 0 | 0 (0.0%) | 0 | 0 (0.0%) |

All reported complications were further adjudicated by the Independent Clinical Events Committee (CEC) for relation to the MR Scan, and relation to the ImageReady System.

All adverse events were reviewed by an independent committee, the SAMURAI Data Monitoring Committee (DMC). During the course of the SAMURAI study, the DMC did not identify any serious risks to subjects.

There were no complications reported related to the protocol required scan; however, 2.8% (5 of 180) of patients experienced an observation related to the

protocol required scan, which were reported under Protocol Testing in the table above. No patients (zero of 48) experienced an adverse event related to a medically necessary MRI.

**Deaths that occurred in the PMA clinical study – SAMURAI**

As of February 17, 2016, sixteen SAMURAI subjects had died (4.4% of all enrolled subjects). All deaths were reviewed and classified by the CEC. No deaths were attributed to the MRI scan.

**Table 42** provides information on Subject Death by Cause. The cause of death described in this table was defined by the SAMURAI CEC.

**Table 42: Study Deaths** *(N = 363 Enrolled Subjects)*

| | | MRI-Related | | System-Related | |
|---|---|---|---|---|---|
| **CEC Adjudicated Cause of Death** | **Classification N (%)** | **Yes N (%)** | **Unknown N (%)** | **Yes N (%)** | **Unknown N (%)** |
| Non Cardiac | 7 (1.9%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Cardiac: Arrhythmic | 1 (0.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Cardiac: Ischemic | 1 (0.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Cardiac: Pump Failure | 1 (0.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Cardiac: Unknown | 1 (0.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Unknown | 5 (1.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Total** | **16 (4.4%)** | **0 (0.0%)** | **0 (0.0%)** | **0 (0.0%)** | **1 (0.3%)** |

The death classified as "Cardiac: Unknown" and "System-Related Unknown" by the CEC was reported by the site as likely related to cardiac arrhythmia leading to cardiogenic shock, not to the pulse generator or pacemaker lead.

Due to insufficient source information on five deaths, the CEC was unable to classify the primary organ cause. None of these five were classified as related to the MRI or the system. One of these five deaths was classified by the site as "Sudden Cardiac Arrest." The subject underwent the implant procedure, but at the time of death, no investigational device had been introduced in the subject's body.

The study DMC monitored subjects' death rate until primary endpoint completion. No overall safety concerns regarding subjects' deaths were raised by the study DMC.

2. Effectiveness Results

The analysis of effectiveness was based on evaluation of key effectiveness outcomes (Primary Effectiveness Endpoint 1 and 2) of paired measurements at the MRI Visit and MRI Visit + 1 Month follow-up time points as presented in **Tables**

**43** and **44**. The 347 randomized patients were eligible for endpoint analysis; exact number of patients for each endpoint are described below.

Both effectiveness endpoints were met and are described in detail later in this section.

*PRIMARY EFFECTIVENESS ENDPOINT 1: PRE- VS. 1-MONTH POST-MR SCAN/CONTROL GROUP VISIT PACING THRESHOLD AT 0.5 MS*

The analysis of Primary Effectiveness Endpoint 1 was based on 203 MRI group patients and 101 Control Group patients for the Intention to Treat analysis and 167 MRI group patients and 96 Control Group patients for the Per Protocol analysis that had paired bipolar pacing threshold measurements at a 0.5 ms pulse width collected at the MRI and the MRI Visit + 1 Month follow-up.

Chronic effects from lead heating were assessed through increased pacing threshold at the MRI Visit + 1 Month follow-up. Subjects that had an increase in pacing thresholds ≤ 0.5V (at 0.5 ms) from pre-MR Scan/Control Group Visit to MRI Visit + 1 Month follow-up were considered a success. A success rate was calculated for the MRI and Control Groups. The hypothesis for that endpoint was that the success rate difference between the Control Group and the MRI Group should be less than 10%.

A total of 101 Control Group subjects and 203 MRI Group subjects had paired threshold measurements and were included in the Intention to Treat (ITT) endpoint analysis. The success rate in the Control group was 98.0% and 98.5% in the MRI group, resulting in a difference of -0.5% and an upper one-sided 95% confidence limit of 3.3%. The Farrington-Manning score test resulted in a p-value < 0.0001.

For the per-protocol (PP) analysis, a total of 96 Control Group subjects and 167 MRI Group subjects had paired threshold measurements and met the inclusion criteria. The success rate in the Control group was 97.9% and in the MRI group was 98.2%, resulting in a difference of -0.3% and an upper one-sided 95% confidence limit of 3.9%. The Farrington-Manning score test resulted in a p-value < 0.0001. Endpoints results are presented in **Table 433** and **Figure 13**.

**Table 43: Primary Effectiveness Endpoint 1 Results – Pre- vs. 1-Month Post-MR Scan/Control Group Visit Pacing Threshold at 0.5 ms**

| Analysis Subgroup | Control Group n/N (%) | MRI Group n/N (%) | Difference Control-MRI (Upper One-Sided 95% CI) | p-value |
|---|---|---|---|---|
| Intention to Treat (ITT) | 99/101 (98.0%) | 200/203 (98.5%) | -0.5% (3.3%) | <.0001 |
| Per Protocol (PP) | 94/96 (97.9%) | 164/167 (98.2%) | -0.3% (3.9%) | <.0001 |

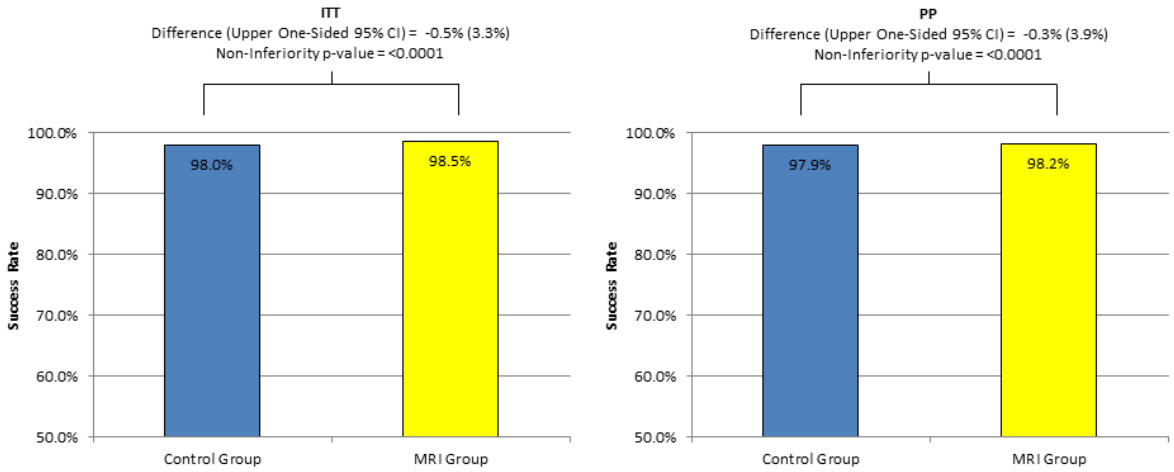


**Figure 13: Primary Effectiveness Endpoint 1: Pacing Threshold Changes (ITT and PP analysis)**

*PRIMARY EFFECTIVENESS ENDPOINT 2: PRE- VS. 1-MONTH POST-MR SCAN/CONTROL GROUP VISIT SENSED AMPLITUDE*

The analysis of Primary Effectiveness Endpoint 2 for right atrial leads was based on 167 MRI group patients and 83 Control Group patients for the Intention to Treat analysis and 135 MRI group patients and 78 Control Group patients for the Per Protocol analysis that had paired sensed amplitude measurements collected at the MRI and the MRI Visit + 1 Month follow-up. The analysis of Primary Effectiveness Endpoint 2 for right ventricular leads was based on 181 MRI group patients and 96 Control Group patients for the Intention to Treat analysis and 152 MRI group patients and 91 Control Group patients for the Per Protocol analysis that had paired sensed amplitude measurements collected at the MRI and the MRI Visit + 1 Month follow-up.

Chronic effects from lead heating were assessed through decreased sensed amplitude at the MRI Visit + 1 Month follow-up. Changes in sensed amplitude pre- and 1-Month post-MR Scan or Control Group Visit were compared between the MRI and Control Groups and analyzed separately by chamber. For atrial sensed amplitudes, a subject was considered a success if the sensed amplitude at the MRI Visit + 1 Month Follow-up remained ≥ 1.0 mV and above 50% of the pre-MR scan/Control Group Visit value. For ventricular sensed amplitudes, a subject was considered a success if the sensed amplitude at the MRI Visit + 1 Month Follow-up remained ≥ 5.0 mV and above 50% of the pre-MR scan/Control Group Visit value. A success rate was calculated for the MRI Group and Control Group.The hypothesis for that endpoint was that the success rate difference between the Control Group and the MRI Group should be less than 10%.

For the Right Atrium, a total of 83 Control Group subjects and 167 MRI Group subjects had paired sensed amplitude measurements and were included in the ITT endpoint analysis. The success rate in the Control group was 96.4% and 96.4% in the MRI group, resulting in a difference of -0.0% and an upper one-sided 95% confidence limit of 4.6%. The Farrington-Manning score test resulted in a p-value of 0.0002. Additionally for the Per Protocol analysis, a total of 78 Control Group subjects and 135 MRI Group subjects had paired sensed amplitude measurements and met the inclusion criteria. The success rate in the Control group was 96.2% and 96.3% in the MRI group, resulting in a difference of -0.1% and an upper one-sided 95% confidence limit of 5.0%. The Farrington-Manning score test resulted in a p-value of 0.0006.

For the Right Ventricle, a total of 96 Control Group subjects and 181 MRI Group subjects had paired sensed amplitude measurements and were included in the ITT endpoint analysis. The success rate in the Control group was 96.9% and 96.1% in the MRI group, resulting in a difference of 0.7% (rounded) and an upper one-sided 95% confidence limit of 5.1%. The Farrington-Manning score test resulted in a p-value is 0.0002. Additionally for the Per Protocol analysis, a total of 91 Control Group subjects and 152 MRI Group subjects had paired sensed amplitude measurements and met the inclusion criteria. The success rate in the Control group was 96.7% and 96.7% in the MRI group, resulting in a difference of -0.0% and an upper one-sided 95% confidence limit of 4.7%. The Farrington-Manning score test resulted in a p-value is 0.0002. Endpoint results are presented in **Table 44**, **Figure 14** and **Figure 15**.

**Table 44: Primary Effectiveness Endpoint 2 Results – Pre- vs. 1-Month Post-MR Scan/Control Group Visit Sensed Amplitude**

| Analysis Subgroup | Chamber | Control Group n/N (%) | MRI Group n/N (%) | Difference Control-MRI (Upper One-Sided 95% CI) | p-value |
|---|---|---|---|---|---|
| ITT | Right Atrium | 80/83 (96.4%) | 161/167 (96.4%) | -0.0% (4.6%) | 0.0002 |
| | Right Ventricle | 93/96 (96.9%) | 174/181 (96.1%) | 0.7% (5.1%) | 0.0002 |
| Per Protocol | Right Atrium | 75/78 (96.2%) | 130/135 (96.3%) | -0.1% (5.0%) | 0.0006 |
| | Right Ventricle | 88/91 (96.7%) | 147/152 (96.7%) | -0.0% (4.7%) | 0.0002 |

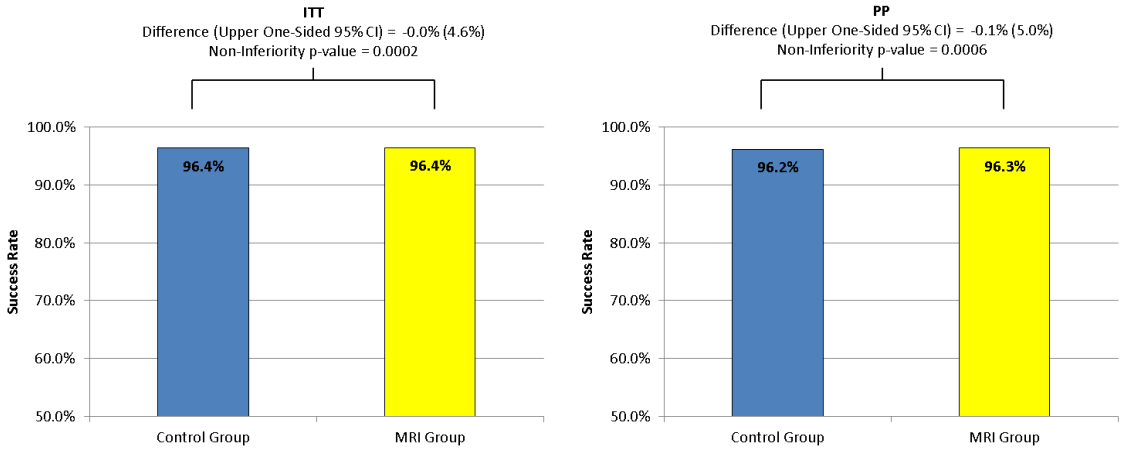


**Figure 14: Primary Effectiveness Endpoint 2: RA Sensed Amplitude Changes (ITT and PP analysis)**

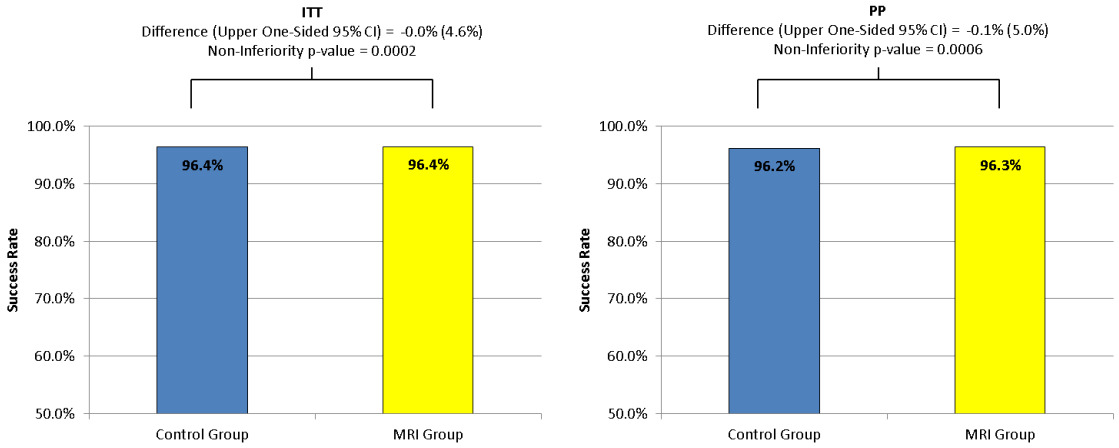


**Figure 15: Primary Effectiveness Endpoint 2: RV Sensed Amplitude Changes (ITT and PP analysis)**

3. Subgroup Analyses

The following preoperative and device characteristics were evaluated for potential association with outcomes: number of leads (1 versus 2), sex, RA lead fixation (active versus passive), RV lead fixation (active versus passive), geography (US versus international), age (<65 versus ≥65), BMI (<30 kg/m$^2$ versus ≥30 kg/m$^2$ ), intermitant second degree AV block, chronic pulmonary disease and idiopathic cardiomyopathy. There were no significant differences observed between subgroups for any endpoint.

4. SAMURAI Clinical Study Conclusion

The safety profile of the ImageReady™ MR Conditional Pacing System was assessed using the MR-related complication free rate and the system-related complication free rate. Both rates met their respective performance goals.

The effectiveness profile of the ImageReady System was assessed by comparing pacing thresholds and sensed amplitude changes before and one month after the MR scan to assess the chronic effect of lead heating. For both parameters, the performance goal was met.

Passing of both safety and effectiveness endpoints indicates that the overall safety and effectiveness profile of the implanted ImageReady System is similar to approved devices.

## F. Financial Disclosure – SAMURAI

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The SAMURAI clinical study included 41 Principal Investigators and 176 Sub-Investigators. Among the investigators involved in the study, 214 have, by way of a signed Certification of Investigator Financial Interest Form, verified that they have no applicable financial arrangement with Boston Scientific defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

The SAMURAI clinical study included five Investigators that have disclosable financial arrangements with SAMURAI disclosed under 21 CFR 54.2, not affecting the outcome of the SAMURAI clinical study. The nature of these disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) is described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 5
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

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

## XIII. SUMMARY OF SUPPLEMENTAL CLINICAL STUDY INFORMATION

### A. SAMURAI Study Support of Accolade Devices

The SAMURAI study also supports the safety and effectiveness of the Accolade devices. The ImageReady System consists of different families of pacemakers (Ingenio MRI or Accolade MRI) with the same family of pace/sense leads (INGEVITY MRI). Regardless of the combination of these system components, the system has the same MRI Conditions of Use. A subset of the pacemaker models from the Ingenio MRI family along with the INGEVITY MRI leads were included in the SAMURAI study to confirm the safety and effectiveness of the ImageReady System when subjected to MR scanning according to the labeled Conditions of Use. This clinical study also confirms safety and effectiveness of the ImageReady System with an Accolade MRI pacemaker. Regarding the clinical study of these devices, Accolade MRI pacemakers are equivalent to Ingenio MRI with respect to design, testing, and clinical endpoints.

The design modifications implemented in comparison to the Ingenio family to create the Accolade family are unrelated to MRI compatibility. Test strategies, bench test methods, computer simulations, preclinical studies, and MRI scanner testing applied to the ImageReady System with Accolade MRI pacemakers are fundamentally the same as those used for the ImageReady System with Ingenio MRI pacemakers. Test data and results also demonstrate the ImageReady System provides protection to patients from potential MRI-related harm with a significant safety margin regardless of the pacemaker model.

The data obtained from the SAMURAI Clinical Study are also applicable to Accolade MRI pacemakers because the clinical protocol and MRI-related outcomes of the clinical study would not be impacted by use of Accolade MRI pacemakers based on the following rationale:

- The primary safety endpoint of the SAMURAI Clinical Study is MRI scan-related complication-free rate from MRI scan through the MRI visit + 1 month follow-up. The SAMURAI Clinical Study confirmed in a clinical setting that MRI-related complications do not occur in patients implanted with an ImageReady System when scanned according to the labeled Conditions of Use. The absence of scan-related complications validates the sufficiency of the broad based non-clinical evaluation performed on Ingenio MRI and subsequently Accolade MRI pacemakers. Boston Scientific's non-clinical evaluation regimen, consistent with ISO/TS 10974, is designed to: a) apply more severe exposure levels than are expected under clinical MRI scanning for each MR field independently, and b) provide monitoring and measurement methods which are more sensitive for detecting device performance anomalies. The combination of severe exposure conditions and stringent performance criteria employed in non-clinical evaluation provides greater opportunity for assessing a wide variety of scenarios with severities beyond what will be found within the limitations of a clinical study.

- The secondary safety endpoint of the SAMURAI study is system-related complication-free rate from implant through 3 months post-implant. This endpoint is not associated with system performance in the MRI environment or MRI scan-related complications. Since the Accolade pacemaker size, shape, and therapy are similar to Ingenio, new pacemaker-related complications are not expected. Since Accolade MRI pacemakers will be paired with the same INGEVITY MRI leads and implanted under standard implant procedures, new lead-related complications are not expected. Differences with Accolade MRI in comparison to Ingenio MRI do not require additional clinical study in regards to this endpoint.

- The primary effectiveness endpoints of the SAMURAI study are pacing threshold and sensed amplitude comparisons pre- and 1 month post-MRI scan. These endpoints are defined to assess lead-related MRI interactions. Since INGEVITY MRI leads will be used with both Ingenio MRI and Accolade MRI pacemakers, differences in Accolade MRI compared to Ingenio MRI do not impact this endpoint.

## B. Summary of the Lead-Related Adverse Event Data Collected Across the INGEVITY and SAMURAI Studies

Lead-related adverse data was collected uniformly across the two studies and is presented in totality in **Table 45** below. The median follow-up time for the INGEVITY study was 32 months, and the median follow-up time for the SAMURAI study was 23 months.

The lead-related adverse event profile is within expectations for a pace/sense lead.

**Table 45: INGEVITY and SAMURAI Lead-Related Adverse Events**

| Adverse Event | Leads Included | INGEVITY | SAMURAI | Total |
|---|---|---|---|---|
| Lead-Related Adverse Event | All Leads | 67/1599 (4.19%) | 33/665 (4.96%) | 100/2264 (4.42%) |
| - Lead-Related Complication | All Leads | 34/1599 (2.13%) | 20/665 (3.01%) | 54/2264 (2.39%) |
| Dislodgment | All Leads | 21/1599 (1.31%) | 8/665 (1.20%) | 29/2264 (1.28%) |
| Perforation/Pericardial Effusion | Active Fixation | 4/1270 (0.31%) | 7/563 (1.24%) | 11/1833 (0.60%) |
| - Perforation | Active Fixation | 0/1270 (0.00%) | 7/563 (1.24%) | 7/1833 (0.38%) |
| - Pericardial Effusion | Active Fixation | 4/1270 (0.31%) | 0/563 (0.00%) | 4/1833 (0.22%) |
| Conductor Coil Fracture | All Leads | 2/1599 (0.13%) | 0/665 (0.00%) | 2/2264 (0.09%) |

As shown in **Table 45** above, two conductor coil fractures occurred in the INGEVITY study. Both events were classified as ventricular lead fractures at the costoclavicular junction, consistent with subclavian crush.

## XIV. PANEL MEETING RECOMMENDATIONS AND FDA'S POST-PANEL ACTION

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

## XV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

### A. Effectiveness Conclusions

The INGEVITY study clinical data demonstrate that the lead performs acceptably. The clinical study met the pre-specified effectiveness endpoints at 3 months of follow-up.

The SAMURAI study clinical data demonstrates that the ImageReady MR Conditional Pacing System performs acceptably while used in the MRI environment. The clinical study met the pre-specified effectiveness endpoints at the MRI + 1 month (3 months post-implant) follow-up.

### B. Safety Conclusions

The risks of the device were assessed using nonclinical laboratory and animal studies as well as data collected in clinical studies conducted to support PMA approval as described above.

The results from the clinical study performed on the INGEVITY Active Fixation and Passive Fixation Pace/Sense Leads demonstrate that this device is suitable for long-term implant. The INGEVITY lead-related adverse event rates are comparable to the rates observed for other market-released pace/sense leads. The INGEVITY clinical study met the pre-specified safety endpoints through the reported follow-up.

The results from the ImageReady™ MR Conditional Pacing System demonstrate that this device is suitable for use in the MR environment. The ImageReady System-related adverse event rates are comparable to the rates observed for other market-released MR Conditional systems. The SAMURAI study met the pre-specified safety endpoints through the MRI + 1 month (3 months post-implant) follow-up.

### C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in clinical studies conducted to support PMA approval as described above. The probable benefit of this family of leads may be summarized as follows:

The INGEVITY lead family, including both MRI and non-MRI leads, has a new design that integrates the handling benefits of coaxial lead design with the small size and redundant insulation features of co-radial designed leads. The coils of the INGEVITY leads are designed to provide mathematically-predicted fatigue characteristics. Other design improvements to characteristics such as the insulation, electrode, lead handling, and lead markings have been made in comparison to previous generations of leads. The INGEVITY leads have undergone extensive bench and animal testing to support a determination of safety and effectiveness.

The purpose of the INGEVITY clinical study was to evaluate the safety and effectiveness of INGEVITY leads in humans. As is summarized in this document, the INGEVITY lead study met its pre-specified safety and effectiveness endpoints, demonstrating a reasonable assurance that the lead is both safe and effective.

The probable benefit of the Image Ready System may be summarized as follows:

Boston Scientific's next generation single and dual chamber pacemakers, the Ingenio MRI and Accolade MRI families, and the next generation pace/sense INGEVITY MRI lead family, are designed to mitigate hazards related to exposure in the MR environment.

The INGEVITY MRI Lead family consists of passive fixation and active fixation leads. Together, the Ingenio MRI or Accolade MRI family of pacemakers and the INGEVITY MRI pace/sense leads comprise the implantable portion of the ImageReady™ MR Conditional Pacing System. The ImageReady System is intended for MR Conditional labeling that allows scanning in First-level Controlled Operating Mode (up to 4 W/kg whole body averaged specific absorption rate (SAR)) and does not require an anatomical isocenter exclusion zone.

The purpose of the SAMURAI clinical study was to confirm the safety, performance, and effectiveness of the ImageReady System in humans when used in the MR environment. The SAMURAI study met its pre-specified safety and effectiveness endpoints, confirming that the ImageReady System is both safe and effective when used in the MR environment according to the Conditions of Use.

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

## D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the devices when used in accordance with their indications for use. There exists no evidence that the lead-related complication rates, dislodgment rates or perforation/pericardial effusion rates significantly differ by study. Therefore, the INGEVITY lead-related adverse event profile in the two studies is comparable.

Additionally, the INGEVITY lead-related adverse event rates are comparable to the rates observed for other market-released pace/sense leads.

Similar to the conclusions drawn for the INGEVITY and SAMURAI studies separately, the combined INGEVITY and SAMURAI data indicate that the overall safety profile of the INGEVITY Lead is similar to approved pace/sense leads.

The preclinical and clinical studies submitted in the PMA application provide a reasonable assurance that the INGEVITY Active Fixation and Passive Fixation Pace/Sense Leads and the ImageReady™ MR Conditional Pacing System are safe and effective.

## XVI. CDRH DECISION

CDRH issued an approval order on April 25, 2016. The final conditions of approval cited in the approval order are described below.

ODE Lead PMA Post-Approval Study – INGEVITY (lead performance) and SAMURAI (multiple MR exposures): The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The study will include two arms 1) the long-term Ingevity lead safety arm and 2) the multiple MRI scan arm.

1. The long-term Ingevity lead safety arm (INGEVITY study) will consist of:

    a. a prospective, multi-center, global, nonrandomized clinical study to characterize chronic lead performance following device implant, as well as a robust process to retrospectively collect implant data for each study subject;
    b. a post-approval study duration of at least 5 years;
    c. a sample size of 1599 leads implanted in 1036 patients that were used for premarket endpoint analyses;
    d. a primary safety endpoint that results in a 95% one-sided lower pointwise confidence limit of the complication-free rate via log-log methodology for all eligible leads will be greater than performance goal of 92.5%;
    e. post-approval study status reporting every six months;
    f. inclusion of full list of complications, failure modes, and definition of terms within the study protocol; and
    g. collection of secondary data including implant data, demographic information, all reported adverse device effects, electrical performance, returned product analysis, extraction experience, and other parameters of interest.

2. The multiple MRI scan arm (SAMURAI study) will consist of:

    a. a total of 351 patients implanted with an ImageReady system that were used for premarket endpoint analyses;

b. a primary safety endpoint that results in 95% one-sided lower pointwise confidence limit of the complication-free rate via log-log methodology will be greater than the performance goal of 95%; and
c. the characterization of the cumulative change in pacing capture thresholds for subjects with multiple (2 or more) MRI scans with an adequate sample size to reach 75 patients with multiple MRI scans.

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

## XVII. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.