Nanostim™ Leadless Pacemaker System

Executive Summary for the Circulatory System Devices Panel of the Medical Devices Advisory Committee

Meeting Date: February 18, 2016

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ADE	Adverse device effect
AHA	American Heart Association
AV	Atrioventricular
BBB	Bundle branch block
BiPAP	Bilevel positive airway pressure
CABG	Coronary artery bypass grafting
CEC	Clinical events committee
CFR	Complication free rate
CI	Confidence interval
CRT	Cardiac resynchronization therapy
CT	Computed tomography
DSMB	Data safety monitoring board
DSP	Dexamethasone sodium phosphate
ESC	European Society of Cardiology
HRS	Heart Rhythm Society
ICD	Implantable cardioverter defibrillator
IDE	Investigational device exemption
IRB	Institutional review board
ITT	Intent to treat
LP	Leadless pacemaker
PA	Pulmonary arterial
PAS	Post-approval study
PMCF	Post-market clinical follow-up
PTCA	Percutaneous transluminal coronary angioplasty
SADE	Serious adverse device effect
SAE	Serious adverse event
SJM	St. Jude Medical
VVIR	Ventricular pacing, ventricular sensing inhibition response and rate-adaptive

1. Executive Summary

1.1 Introduction

Cardiac pacing has been an established therapy for patients with bradyarrhythmias for over 50 years.[1] Pacemaker system designs have undergone continual refinement aimed to reduce size, improve reliability, and expanded functionality. However, all pacemakers currently approved in the United States require leads between the heart and a separate implanted pulse generator to deliver stimulatory impulses and transmit cardiac signals for sensing. Lead-related complications are the most frequent cause of permanent pacemaker system complications,[2, 3] and necessitate reoperation in nearly 4% of pacemaker recipients.[4] All lead designs are subject to complications such as infection, fracture, failure, and venous thrombosis.[5] Lead- related infection is estimated to occur in 1% to 2% of patients[6] (reported incidences range from 0.13% to 12.6%)[7-9] and is associated with substantial morbidity and mortality, including a more than two-fold increase in the rate of in-hospital death for patients with a traditional pacemaker/ implantable cardioverter defibrillator (ICD) infection, compared to those without pacemaker/ICD infection.[2, 10, 11] The pacemaker pulse generator pocket is also a significant source of pacemaker-related complications. In addition to its involvement in pacemaker system infection (in up to 60% of cases, and which often extends to intravascular components of the system),[2] pocket hematoma at the surgical site is common and can lead to local discomfort, prolonged hospital stay, and/or the need for lead and device revision.[12]

These conventional pacemaker complications have led to an interest in developing a leadless means to provide bradycardia support. A pacing system that eliminates the lead as a conduit for energy transfer (“leadless pacemaker”), and the need for a separate generator and pocket could provide several advantages over existing systems.

1.2 Nanostim Leadless Pacemaker System Overview

The Nanostim leadless pacemaker (LP), shown in **Figure 1-1**, provides bradycardia pacing as a pulse generator with built-in battery and electrodes, for implantation in the right ventricle.

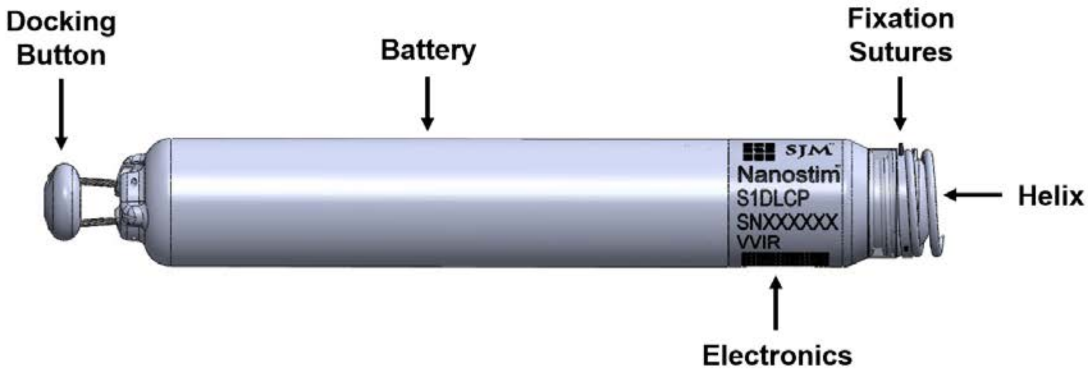


Figure 1-1: Nanostim Leadless Pacemaker

As a leadless pacemaker, it does not need a connector, pacing lead, or pulse generator pocket. A distal non-retractable, single-turn helix affixes the Nanostim LP to the endocardium. Sensing, pacing and communication with the external programmer occur between a distal electrode near the helix and the external can of the Nanostim LP. The pacemaker's proximal end has a feature that enables it to be docked to delivery and retrieval catheters, which provides for repositioning and retrieval capability.

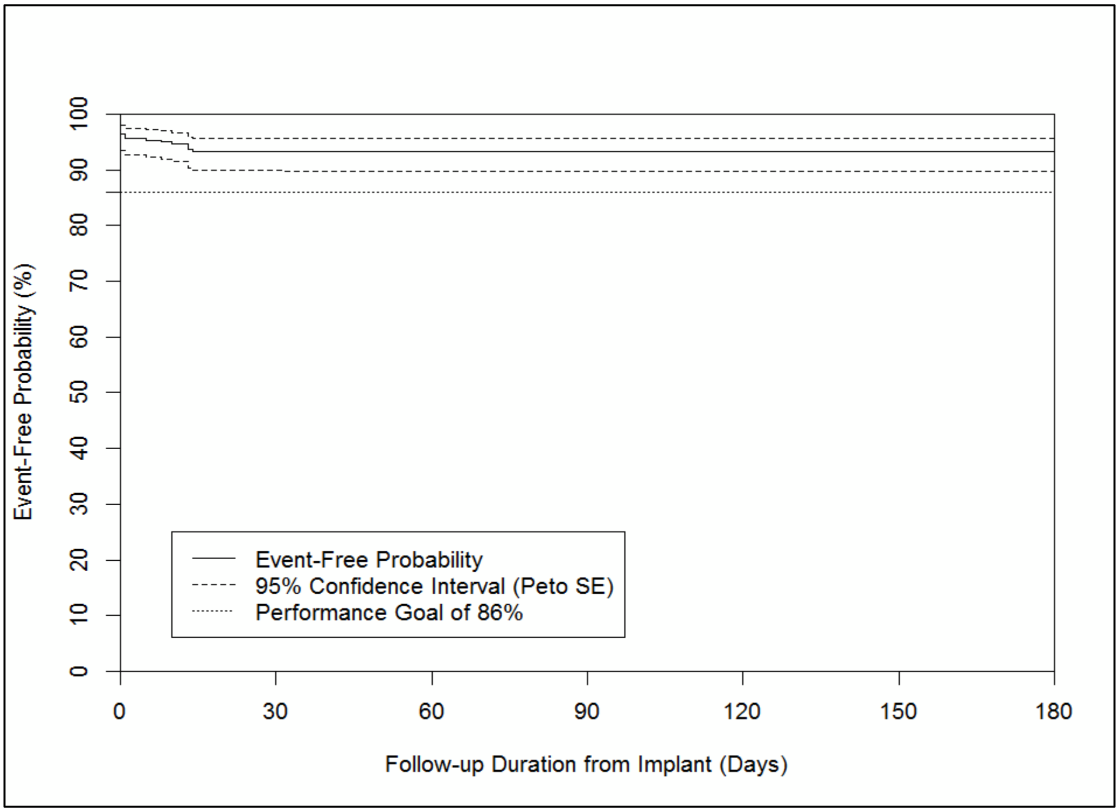
1.3 Effectiveness and Safety Outcomes in Pivotal Study

The Leadless II Investigational Device Exemption (IDE) study is a prospective, non-randomized, single-arm, multi-center pivotal clinical trial designed to evaluate the safety and effectiveness of the Nanostim LP System. The study is being conducted at 56 centers in the US, Canada and Australia. The total number of patients to be enrolled is 667. Consistent with information published in the New England Journal of Medicine, data presented herein include 6-month data for the first 300 patients who made up the primary cohort, as well as for the total cohort of 526 patients who were enrolled as of June 4, 2015.[13]

Based on the primary analysis cohort of the first 300 patients with 6-month follow-up, the primary effectiveness endpoint and primary safety endpoint were both met. The Nanostim LP was successfully implanted in 95.8% of patients.

- Effectiveness through 6 months was assessed by comparing the percent of patients with both an acceptable pacing threshold (≤2.0V at 0.4msec) and an acceptable sensing amplitude (R-wave ≥5.0mV, or a value at least as great as the value at implantation) to a performance goal of 85%, based on historical data.
- The primary effectiveness endpoint was met, with 90% of patients (270/300) meeting the effectiveness criteria [95% confidence interval (CI): 86.0 – 93.2%; p=0.007].
- Safety through 6 months was assessed by comparing the percent of patients without a serious adverse device effect (SADE) to the performance goal of 86%, based on historical data.
- The primary safety endpoint was met with 93.3% of patients (280/300) meeting the safety criteria (95% CI: 89.9 – 95.9%; p<0.001)

At 6-months, serious adverse device effects (SADEs) were observed in 6.7% of patients in the primary analysis cohort. Events included device dislodgement with percutaneous retrieval in 1.7% of patients, cardiac perforation in 1.3% of patients, and pacing-threshold elevation requiring percutaneous retrieval and device replacement in 1.3% of patients. As can be observed in **Figure 1-2**, showing the Kaplan-Meier analysis of freedom from SADEs, all SADEs occurred within the early post-operative period. Results in the total cohort of 526 patients were similar to those in the primary analysis cohort of 300 patients. The results of the Leadless II study provide reasonable assurance of safety and effectiveness of the Nanostim Leadless Pacemaker.



Data Category	Follow-up Duration from Implant (Days)						
	0	**30**	**60**	**90**	**120**	**150**	**180**
At Risk	300	278	267	265	264	263	262
Event	11	20	20	20	20	20	20
Survival	96.3%	93.3%	93.3%	93.3%	93.3%	93.3%	93.3%
95% CI	(93.5%, 97.9%)	(89.8%, 95.6%)	89.8%, 95.7%)	(89.7%, 95.7%)	(89.7% 95.7%)	(89.7%, 95.7%)	(89.7%, 95.7%)

Figure 1-2: Kaplan-Meier Analysis of Primary Safety Endpoint

1.4 Proposed Post-Approval Study and Training Program

In order to optimize and monitor outcomes in the commercial setting, St. Jude Medical (SJM) has proposed a post-approval study as well as mandatory physician training.

1.4.1 Nanostim Post-Approval Study Proposal

In order to gather further long-term safety data on the Nanostim LP, SJM is proposing to conduct a 7-year follow-up, 1700 patient post-approval study (PAS). Data collected will help to characterize acute and long term safety, as well as the management of patients at the time of device replacement or deactivation. The proposed PAS is a prospective, non-randomized, multi-center clinical study designed to evaluate the long-term safety of the Nanostim™ Leadless Pacemaker in patients with a ventricular pacing, ventricular sensing inhibition response and rate-adaptive (VVIR) pacing indication.

1.4.2 Nanostim Training Program

St. Jude Medical has developed a phased, standardized methodology for providing physicians with education and training on how to safely implant a Nanostim LP, and care for their Nanostim implanted patients. The goal of the training program is to ensure that physicians are proficient with the implanting technique and optimize positive clinical outcomes for the patients.

The training program will be mandatory, requiring completion of multiple modules prior to receiving certification. The training is similar to that provided to the physicians who participated in the Leadless II study, and has been revised to include key learnings from worldwide clinical experience of the Nanostim LP.

There are multiple phases to the training, encompassing 7 modules, as shown below:

- Nanostim Didactic Training (Module 1)
- Hands-On Training
    - Implant Demonstration with Catheter (Module 2)
    - Animal Lab Training (Module 3) **or** Virtual Reality Training (Module 5)
    - Video Compendium (Module 4)
- Case Observation (live or recorded; Module 6a)
- Ten Procedures with Technical and Implant Support and In-Case Training by SJM Certified Personnel (Module 6b)
- Site-Training and onboarding (Module 7)

To participate in the training program, physicians must be qualified to implant pacemakers and have an established practice affiliation with an institution that has resources to supported leadless pacemaker implantation.

1.5 Benefit-Risk Assessment

Leadless pacing provides many benefits over conventional transvenous pacemaker systems. The data collected during clinical studies support the safety and effectiveness of the Nanostim LP System when used in accordance with the indications for use. No unanticipated serious adverse device effects have occurred to date, and the device has performed as intended. Moreover, electrical measurements show that pacing thresholds, R-wave amplitudes, and pacing impedances are within the expected range and the mean projected device longevity at 6 months is approximately 15 years. Current experience has demonstrated that the device can be chronically retrieved without SADEs.

Clinical risks most frequently encountered with transvenous pacemaker systems are related to the pacemaker pocket and the transvenous lead, therefore they are inherently not relevant to the Nanostim LP System. The overall six-month complication rate of the Nanostim LP including perforation and dislodgement, was found to be similar to commercially available transvenous pacemakers and leads.[4,14,15] The overall long term complication rate of the Nanostim LP is expected to be superior to commercially available transvenous systems due to the elimination of the lead, which is subject to continued wear and potential complications over the course of time. Beyond the service life of the Nanostim LP, the ability to chronically retrieve the device has the potential to further reduce long-term risks to the patient. After retrieval of the Nanostim LP, no component remains in the heart that could create a risk for infection or occupy space within the heart and the vasculature.

In summary, the benefits of the Nanostim LP System outweigh the risks. The observed safety and effectiveness of the Nanostim LP support its use as an alternative to transvenous pacemakers in patients indicated for single-chamber ventricular pacing. A robust training program will support safe use of the Nanostim LP upon commercialization and event rates will continue to be monitored in post-approval studies to ensure this balance remains favorable.

Appendix A includes the St. Jude Medical perspective on the Agency's specific discussion questions for the Advisory Committee.

2. Overview of the Nanostim Leadless Pacemaker

2.1 Proposed Indication Statement

The proposed intended use of the Nanostim Leadless Pacemaker is consistent with that of commercially available single chamber rate responsive pacemakers.

Ventricular Pacing is indicated for patients with significant bradycardia and

- Normal sinus rhythm with rare episodes of A-V block or sinus arrest
- Chronic atrial fibrillation
- Severe physical disability

Rate-Modulated Pacing is indicated for patients with chronotropic incompetence, and for those who would benefit from increased stimulation rates concurrent with physical activity. Chronotropic incompetence has not been rigorously defined. A conservative approach, supported by the literature, defines chronotropic incompetence as the failure to achieve an intrinsic heart rate of 70% of the age-predicted maximum heart rate or 120 bpm during exercise testing, whichever is less where the age-predicted heart rate is calculated as 197 - (0.56 x age).

2.2 Background

Cardiac pacing has been an established therapy for patients with bradyarrhythmias for over 50 years.[1] Pacemaker system designs have undergone continual refinement aimed to reduce size, improve reliability, and expand functionality. However, all pacemakers currently approved in the United States require leads between the heart and a separate implanted pulse generator to deliver stimulatory impulses and transmit cardiac signals for sensing. Lead-related complications are the most frequent cause of complications of permanent pacemaker systems,[2,3] and necessitate reoperation in nearly 4% of pacemaker recipients.[4] All lead designs are subject to complications such as infection, fracture, failure, and venous thrombosis.[5] Lead-related infection is estimated to occur in 1% to 2% of patients[6] (reported incidences range from 0.13% to 12.6%)[7-9] and is associated with substantial morbidity and mortality, including a more than 2-fold increase in the rate of in-hospital death for patients with a traditional pacemaker/ implantable cardioverter defibrillator (ICD) infection, compared to those without pacemaker/ICD infection.[2,10,11] The presence of infection requires complete system extraction, a procedure that is itself associated with a 1-4% rate of major complications, including tearing of the veins, right atrium, right ventricle, cardiac tamponade, hemothorax, pulmonary embolism, and death.[16-19] Other lead-related complications, including lead fracture, failure, or malfunction, are the result of the repeated mechanical stresses placed on the lead during the cardiac cycle, and their occurrence (1% to 3% at 5 years) is associated with adverse advents and the need for repeat procedures.[20] In addition, transvenous leads cross the tricuspid valve en route to the right ventricle, and can damage the valve or interfere with its function. Lead-induced tricuspid regurgitation has been reported in 7% to 39% of patients following endocardial lead implantation,[21-23] and the incidence of severe lead-induced regurgitation may increase with the duration of the implant,[24] and in severe cases can even cause right heart failure necessitating tricuspid valve surgery. This indication was responsible for 2.8% of all tricuspid valve operations performed at the Mayo Clinic over a 10 year period, with most cases recognized in the final two years of the study.[25]

The pacemaker pulse generator pocket is also a significant source of pacemaker-related complications. In addition to its involvement in pacemaker system infection (in up to 60% of cases, and which often extends to intravascular components of the system),[2] pocket hematoma at the surgical site is common and can lead to local discomfort, prolonged hospital stay, and/or the need for lead and/or device revision.[12] Pocket hematoma is reported in 5% to 10% of patients receiving implanted cardiac rhythm management devices.[12,26] In one study of 935 patients, the occurrence of hematoma increased median length of hospital stay from 2 to 4 days ($p=0.004$),[12] and patients with a hematoma were more likely to require surgical intervention (5.6% vs. 1.2%) and to have late complications (18% vs. 1.9%), including infection, recurrent hematoma, and lead dislodgement.

These potential conventional pacemaker complications have led to an interest in development of a leadless means to provide bradycardia support. A pacing system that eliminates the lead as a conduit for energy transfer (“leadless pacemaker”), and the need for a separate generator and pocket could provide several advantages over existing systems, including:

- No lead-related infections
- No lead fractures, lead insulation or connector problems
- No risk of lead-induced tricuspid regurgitation
- No surgery to create subcutaneous pulse generator pocket
- Greater patient comfort postoperatively and elimination of scars and generator bulge
- No pocket-related infection or hematoma

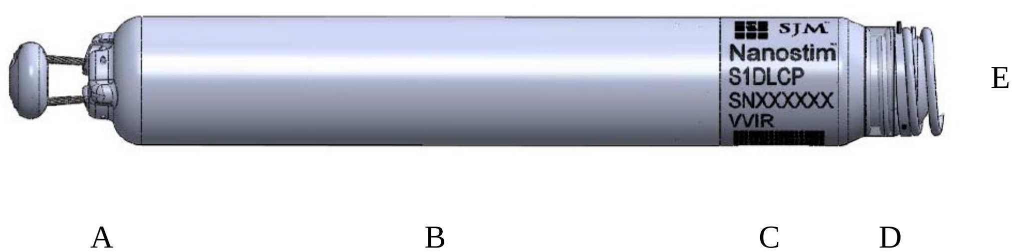
2.3 Device Description

The Nanostim LP provides bradycardia pacing as a pulse generator with built-in battery and electrodes, for permanent implantation in the right ventricle. As a leadless pacemaker, it does not require a connector, pacing lead, or pulse generator pocket. A distal non-retractable, single-turn helix affixes the Nanostim LP to the endocardium. Sensing, pacing and communication with the external programmer occur between a distal electrode near the helix and the external can of the Nanostim LP. The pacemaker’s proximal end has a feature to enable it to be docked to delivery and retrieval catheters, which provides for repositioning and retrieval capability.

2.3.1 Leadless Pacemaker

The pacemaker communicates bi-directionally with the programmer via electrical signals conducted between the implanted Nanostim LP's electrodes and skin electrodes applied to the patient's chest and connected to the programmer. Consequently the pacemaker transmits signals using circuits and electrodes already provided for pacing, with data encoded in pulses delivered during the heart's refractory period.

The pacemaker senses right-ventricular blood temperature to provide an increase in pacing rate with increased metabolic demand. The tip electrode includes dexamethasone sodium phosphate that is intended to promote low acute and chronic stimulation thresholds by suppressing the local inflammatory response to a foreign body. **Figure 2-1** shows mechanical characteristics of the Nanostim LP. The pacemaker has a length of 42 mm and a maximum outer diameter of 6 mm. **Figure 2-2** shows the Nanostim LP in place attached to the right ventricle. The surface area of the device is approximately 9 cm^2, or about a third of the surface area of a typical lead. Extensive animal lab experience with histopathology supports that the LP is non-thrombogenic.



A. Docking Interface button with cables.

B. Ring electrode.

C. Insulated nosecone.

D. MP35N fixation helix with nylon sutures for additional fixation.

E. Titanium nitride (TiN) coated platinum-iridium (Ptlr) electrode with steroid (proximal to helix)

Figure 2-1: Nanostim Leadless Pacemaker

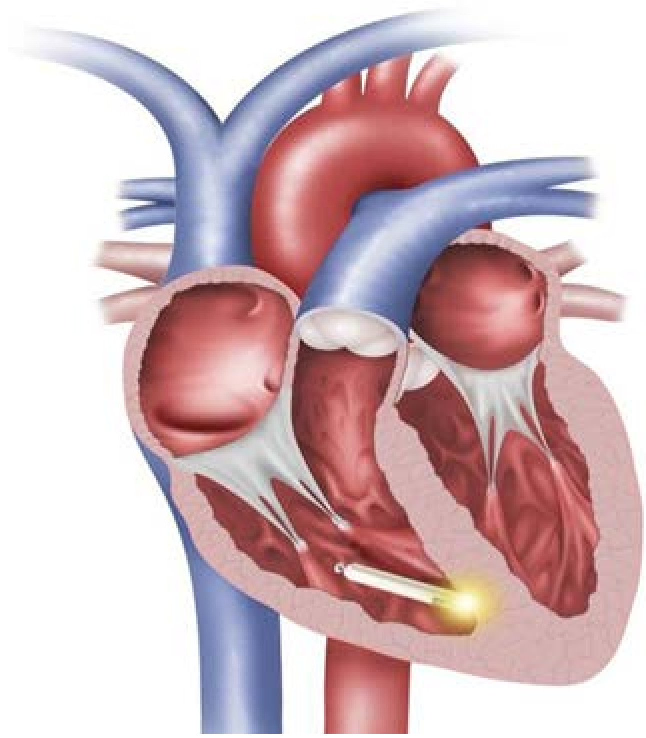


Figure 2-2: Nanostim LP Attached to Right Ventricle

2.3.2 Delivery catheter

The Nanostim Delivery Catheter System, shown in **Figure 2-3** includes a deflectable delivery catheter, designed to allow introduction of the Nanostim LP via a percutaneous access site in the femoral vein. The delivery catheter provides a means for a single operator to:

- Advance the Nanostim LP from an access site in the groin (utilizing minimally invasive techniques) through the femoral vein to the right ventricle
- Protect the Nanostim LP helix and electrode during delivery
- Position the Nanostim LP and rotate it to affix the helix
- Undock the Nanostim LP from the delivery catheter leaving the pacemaker tethered to the delivery catheter, to measure thresholds without force from the catheter
- Re-dock to the catheter, unscrew and reposition the Nanostim LP if necessary for acceptable thresholds
- Undock from the Nanostim LP, leaving it implanted, and disconnect it from the tether

Apart from the docking mechanism, the delivery catheter and its control system (handle) have the same operating principle as a conventional steerable catheter and control system. A photograph of the handle is shown in **Figure 2-4**. The system includes an introducer, a guide catheter, and an ePTFE sleeve to protect the fixation helix and electrode.

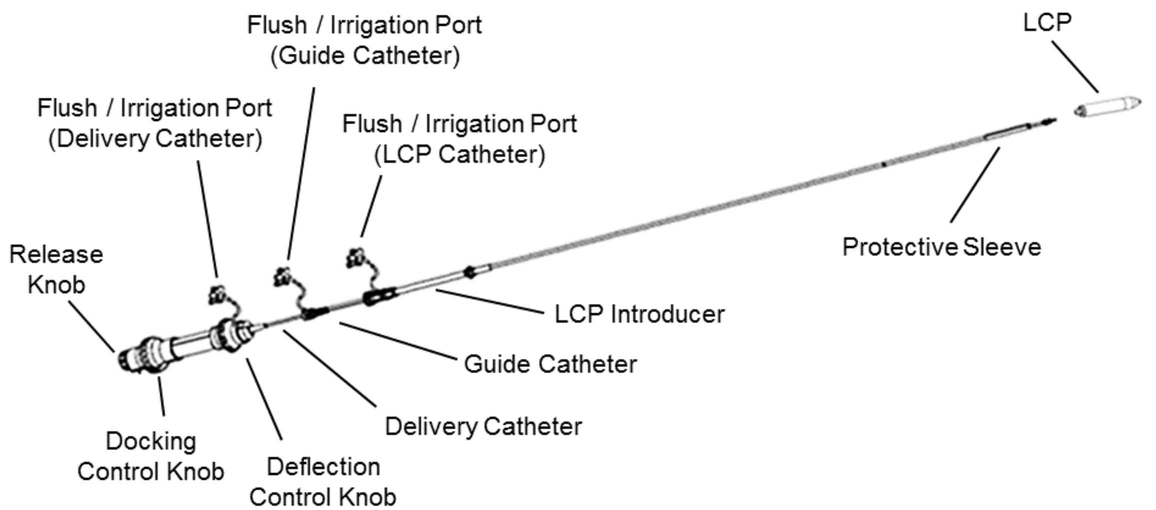


Figure 2-3: Nanostim Delivery System Catheter

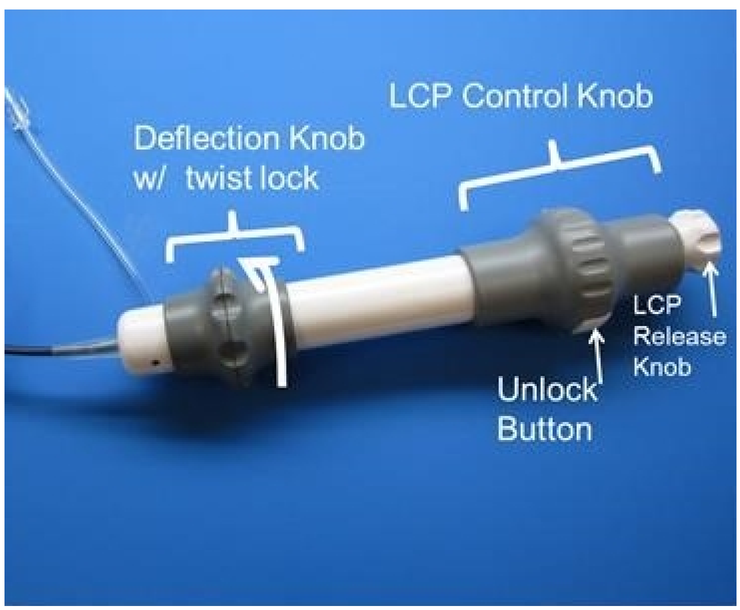


Figure 2-4: Picture of Catheter Handle

2.3.3 Nanostim Programmer Link Connected to the Merlin Programmer

In order to program the Nanostim LP, the Nanostim Programmer Link interfaces with the FDA approved St. Jude Medical Merlin Patient Care System Programmer via USB interface. The Nanostim Link uploads Nanostim software to the Merlin programmer and provides an interface between the programmer and standard ECG electrodes placed on the subject's torso, for two-way communication with the implanted pacemaker and display of the surface ECG.

The Merlin programmer displays the patient's ECG and status of the implanted Nanostim LP. The link sends commands to change pacemaker parameter settings as directed by a user via conducted communication with sub-threshold pulses applied to the skin electrodes. Apart from this conducted communication, it has the same operating principle as a conventional pacemaker programmer.

2.3.4 Nanostim Retrieval Catheter System

The Nanostim Retrieval Catheter System is provided separately from the Nanostim LP System, but a description is provided here. The Nanostim LP is designed to be fully retrievable. The Nanostim Retrieval Catheter System includes a deflectable retrieval catheter and guide catheter with two variants: one which includes a tri-loop snare at the distal tip, and the other which includes a single-loop snare at the distal tip. The retrieval catheter snares are used to engage the docking feature on the proximal end of the Nanostim LP, mate the retrieval catheter with the docking cap, unscrew it, and retrieve it.

Using standard percutaneous access techniques to enter the femoral vein, the retrieval catheter allows a single operator to:

- Mate with the proximal button of the Nanostim LP from an access site in the groin through the femoral vein to the right ventricle
- Dock to the Nanostim LP
- Rotate the Nanostim LP to unscrew the helix from the endocardium
- Protect the pacemaker helix and electrode during retrieval
- Extract the Nanostim LP through the access site in the groin

Apart from the accessing and docking features, the retrieval system has the same operating principle as a conventional steerable catheter and control system (handle). The retrieval catheters have lumens for irrigation. The catheters are not intended to be delivered over a guidewire and not compatible with any size wire.

All components and subassemblies of the tri-loop and single-loop retrieval catheters are identical, with the exception of the innermost snare subassembly. **Figure 2-5** and **Figure 2-6** show mechanical characteristics for the single-loop and tri-loop retrieval catheters.

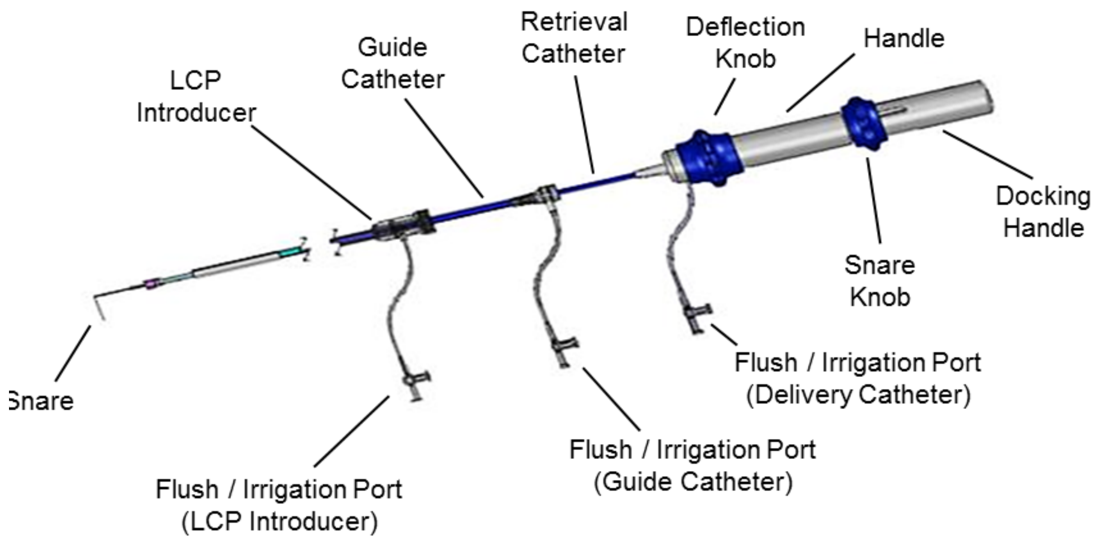
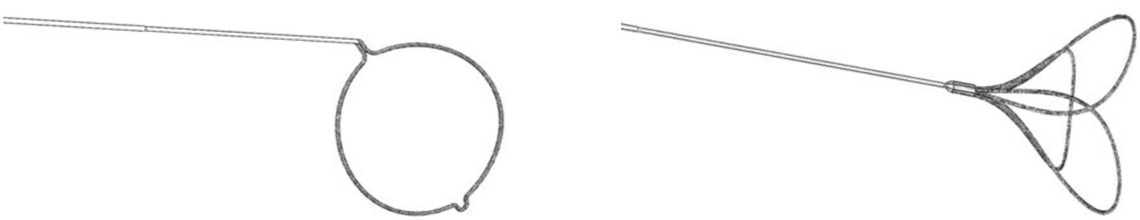


Figure 2-5: Nanostim Retrieval Catheter Configuration

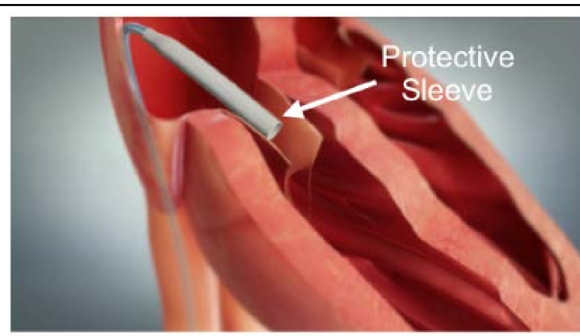


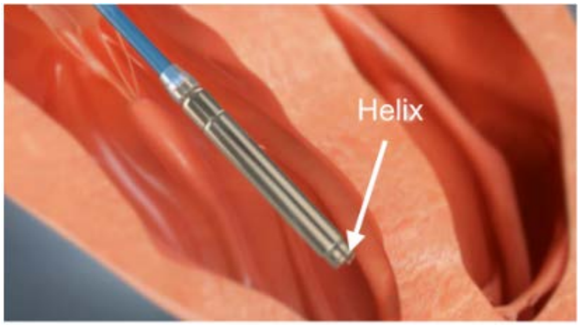
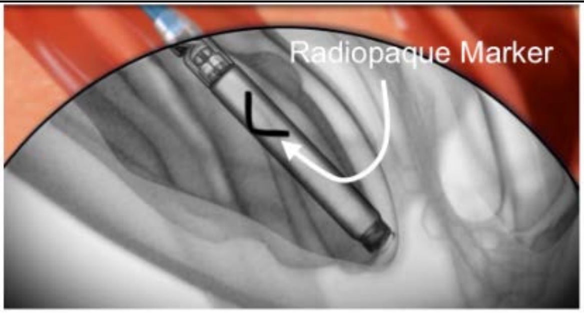
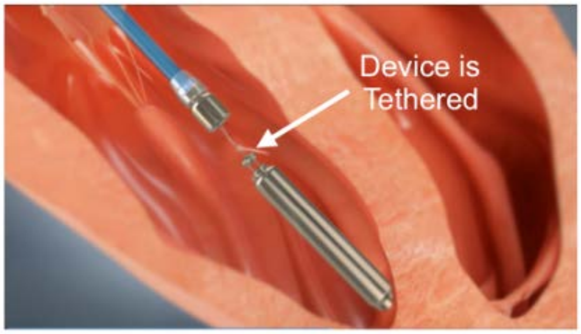
Single-loop snare **Tri-loop snare**

Figure 2-6: Retrieval Catheter Single-Loop or Tri-Loop Design

2.4 Nanostim Placement Procedure

The Nanostim LP, affixes to the right ventricular endocardium. The insertion procedure is as follows:[13]

1. The Nanostim LP, with the protective sleeve covering the helix, is advanced through the femoral vein in to the right atrium and the delivery catheter is deflected and advanced through the tricuspid valve, into the right ventricle.	

2. Contrast in injected through the sleeve to confirm positioning within the right ventricle. The protective sleeve is retracted to expose the device helix, and the leadless pacemaker is advanced until it reaches the endocardium at the lower septum.	
3. Forward pressure is gently applied, and under fluoroscopy, the control knob is slowly turned until the radiopaque marker has rotated 1 to 1.25 turns.	
4. The Nanostim LP is undocked from the delivery catheter to put the device in tether mode. The catheter is gently deflected and undeflected to confirm fixation and test sending and pacing thresholds while the device is naturally interacting with the beating heart.	
5. If necessary, the device is repositioned by re-docking the delivery catheter and unscrewing the helix. After slightly pulling back the device, steps 3 and 4 are repeated. Once properly positioned, the device is released.	

3. Pivotal Study Design and Outcomes

3.1 Study Overview

The pivotal study for the Nanostim Leadless Pacemaker System is the Leadless II IDE study. It is a prospective, non-randomized, single-arm, multi-center clinical study designed to evaluate the safety and effectiveness of the Nanostim Leadless Pacemaker System.

The study is being conducted at 56 centers in the US, Canada and Australia. The total number of patients to be enrolled is 667. Consistent with information published in the New England Journal of Medicine, data presented herein include 6-month data for the first 300 patients who made up the primary cohort, as well as for 526 patients who were enrolled as of June 4, 2015.[13]

3.2 Key Study Findings

The Nanostim LP was successfully implanted in 95.8% of patients. Based on the primary analysis cohort of the first 300 patients with 6-month follow-up, the primary effectiveness endpoint and primary safety endpoint were both met:

- Effectiveness through 6 months was assessed by comparing the percent of patients with both an acceptable pacing threshold (≤2.0V at 0.4msec) and an acceptable sensing amplitude (R-wave ≥5.0mV, or a value at least as great as the value at implantation) to a performance goal of 85%, based on historical data.
- The primary effectiveness endpoint was met, with 90% of patients (270/300) meeting the effectiveness criteria (95% CI: 86.0 – 93.2%; p=0.007).
- Safety through 6 months was assessed by comparing the percent of patients without a serious adverse device effect (SADE) to the performance goal of 86%, based on historical data.
- The primary safety endpoint was met with 93.3% of patients (280/300) meeting the safety criteria (95% CI: 89.9 – 95.9%; p<0.001)

At 6-months, SADEs were observed in 6.7% of patients in the primary analysis cohort. (The SADE definition is detailed in Section 3.3.3.2). Events included device dislodgement with percutaneous retrieval in 1.7% of patients, cardiac perforation in 1.3% of patients, and pacing-threshold elevation requiring percutaneous retrieval and device replacement in 1.3% of patients. Results in the total cohort of 526 patients were similar. The results of the Leadless II study provide reasonable assurance of safety and effectiveness of the Nanostim leadless pacemaker.

3.3 Study Design

3.3.1 Inclusion and Exclusion Criteria

3.3.1.1 Inclusion Criteria

To be enrolled in the Leadless II study, patients had to meet the following criteria:

1. Had one of the clinical indications before device implant in adherence with Medicare, American College of Cardiology (ACC), American Heart Association (AHA), Heart Rhythm Society (HRS), and European Society of Cardiology (ESC) single chamber pacing guidelines including:
   - Chronic and/or permanent atrial fibrillation with 2nd or 3rd degree atrioventricular (AV) or bifascicular bundle branch block (BBB), including slow ventricular rates (with or without medication) associated with atrial fibrillation; or
   - Normal sinus rhythm with 2nd or 3rd degree AV or BBB and a low level of physical activity or short expected lifespan (but at least one year); or
   - Sinus bradycardia with infrequent pauses or unexplained syncope with EP findings
2. At least 18 years of age
3. Had a life expectancy of at least one year
4. Not enrolled in another clinical investigation
5. Willing to comply with clinical investigation procedures and agrees to return for all required follow-up visits, tests, and exams
6. Had been informed of the nature of the study, agrees to its provisions and has provided a signed written informed consent, approved by institutional review board (IRB)
7. Not pregnant and did not plan to get pregnant during the course of the study

3.3.1.2 Exclusion Criteria

Patients were not eligible for the Leadless II study if they had any of the following:

1. Known pacemaker syndrome, has retrograde ventriculoatrial conduction, or suffers a drop in arterial blood pressure with the onset of ventricular pacing
2. Allergic or hypersensitive to < 1mg of dexamethasone sodium phosphate (DSP)
3. Mechanical tricuspid valve prosthesis
4. Pre-existing pulmonary arterial (PA) hypertension (PA systolic pressure exceeds 40 mmHg or right ventricle systolic pressure as estimated by echo exceeds 40 mmHg), or significant

physiologically-impairing lung disease (have severe pulmonary disease producing frequent hospitalizations for respiratory distress or requiring continuous home oxygen)

5. Pre-existing endocardial pacing or defibrillation lead
6. At the time of enrollment, implanted with either a transvenous or subcutaneous ICD or cardiac resynchronization therapy (CRT) device
7. Implanted vena cava filter
8. Evidence of thrombosis in one of the veins used for access during the procedure
9. Recent cardiovascular or peripheral vascular surgery within 30 days of enrollment*
10. Implanted leadless cardiac pacemaker

*If a patient had any of the following cardiovascular or peripheral vascular procedures performed within 30 days of screening, the patient could not be enrolled in the study:

- Percutaneous valvular correction ≤30 days
- Femoral or abdominal vascular procedure involving incisional access ≤ 30 days
- Peripheral or arterial endovascular procedure or surgery ≤ 30 days
- Cardiac surgery ≤ 72 hours with ongoing complications, ongoing mediastinal drainage, or re-do sternotomy attributed to bleeding ≤ 30 days
- Tricuspid valve replacement or annuloplasty ≤ 30 days
- Any endovascular procedure with specified complication ≤ 30 days
- Femoral access site-vascular complication including hematoma requiring transfusion, surgical intervention or prolongation of hospitalization, arterio-venous fistula, pseudoaneurysm or tear
- New pericardial effusion more than trivial/mild, or requiring percutaneous/surgical drainage
- Acute deep venous thrombosis

3.3.2 Study Procedures

The first patient was enrolled on February 4, 2014. The cut-off date for enrollment included in this report is June 4, 2015 and the cut-off date for follow-up data included in this report is June 29, 2015. A total of 526 patients were enrolled at 56 investigational sites worldwide as of the enrollment cut-off date. Investigational sites and enrollment numbers are provided in Appendix B.

Study enrollment was defined as signing an approved IRB informed consent and undergoing an implant attempt with the Nanostim LP. After the device was implanted and before the patient was discharged from the hospital the pacemaker was interrogated and the patient underwent chest radiography and standard 12-lead electrocardiography. Pacemaker programming was left to the physician's discretion. Following successful implant, patient follow-up occurred at pre-discharge, 2 weeks, 6 weeks, 3 months, and 6 months after implant, and every 6 months thereafter until study completion at 7 years post-implant. Patients whose Nanostim LP implant attempt was unsuccessful were followed for 30 days and then withdrawn from the study.

An independent Clinical Events Committee (CEC), which was blinded to the site and patient identifiers, adjudicated and classified all reported adverse events and deaths. The CEC's role in adjudicating adverse events was to determine a) the relationship of an event as either device and/or procedure related and b) the severity of an event (serious or not). The CEC was chaired by Dr. Joshua Cooper of Temple University in Pennsylvania. In addition to the CEC, an independent Data Safety Monitoring Board (DSMB) had oversight of the study and reviewed study data on a regular basis.

3.3.3 Study Effectiveness Endpoints

3.3.3.1 Primary Effectiveness Endpoints

The primary effectiveness endpoint was a 6-month composite success rate evaluating pacing thresholds and R-wave amplitudes, where pacing threshold had to be $\leq$ 2V at 0.4 msec and R-wave amplitude had to be $\geq$ 5.0 mV or a value equal to or greater than the value at implantation. For pacemaker dependent patients or patients who underwent AV node ablation, no R-wave can be measured at the 6-month visit; in such patients, success was based on pacing threshold alone.

This composite endpoint was compared to a performance goal of 85%. The effectiveness performance goal is consistent with findings from another St. Jude Medical pacemaker study (NCT 01576016), where 88% of patients had a pacing threshold <2V at 0.5ms and R-wave >5 mV (95% CI of 85.8% to 90.1%). Considering the lower confidence bound, a performance goal of 85% for the 6-month composite success rate is justified.

3.3.3.2 Primary Safety Endpoint

The primary safety endpoint evaluated the 6-month complication-free rate (CFR). Complication was defined as a device- or procedure-related serious adverse event, including any adverse event that prevented initial implantation. Serious adverse events (SAEs) were defined as any untoward medical occurrence that led to death or to a serious deterioration in the health of a patient that resulted in life-threatening illness or injury, permanent impairment of a body structure or a body function, inpatient or prolonged hospitalization, or a medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

All adverse events were adjudicated by the CEC. An SAE was classified as a SADE if the event was adjudicated as attributable to the investigational device or procedure. It is important to note when assessing adverse events that the investigational device consisted of any of the components, including the Nanostim LP as well as the delivery catheter system. Also of note, the definition of SADE used in this study differs from the definition of "major complication" used to characterize the safety of another leadless pacemaker.[15]

The complication-free rate was compared to a performance goal of 86%. The safety performance goal is in line with that obtained from two pacemaker studies.[14, 27] In one study of 143 patients who received single-chamber pacemakers, the 3-month complication rate was 11.2% with a 95% CI of 5.9% to 16.4%.[27] In the prospective FOLLOWPACE study of 1516 patients, the 2-month complication rate was 10.5%, with a 95% CI of 9.0 to 12.1% not including any atrial lead complications.[14] Utilizing the midpoint of the 95% upper confidence bounds, a complication rate of approximately 14% is an appropriate performance goal. Noting that the device-related complications in the FOLLOWPACE study occurred at a much lower rate after 3 months post-implantation, a performance goal of 86% for the six month complication free rate is justified.

3.3.4 Summary of Statistical Analyses

A sample size of 300 patients was determined to provide 90% power at a two-sided 5.0% significance level, to show rates of safety and effectiveness would be superior to predetermined performance goals.

The primary effectiveness hypothesis is based on the proportion of patients experiencing success, with success defined as having a pacing threshold voltage $\leq$ 2.0 V at 0.4 msec at 6-month visit <u>and</u> sensed R-wave amplitude either $\geq$ 5.0 mV at the 6-month visit or $\geq$ value at implant. The rate is estimated as a binomial proportion and the 95% CI is calculated using the Clopper-Pearson exact method. The null hypothesis is rejected at the 2.5% significance level if the lower bound of this CI exceeds the performance goal of 85%.

The primary safety hypothesis is based on the complication free rate at 6 months. The CFR is estimated as a binomial proportion and the 95% CI of CFR is calculated using the Clopper-Pearson exact method. The null hypothesis is rejected at the 2.5% significance level if the lower bound of this CI exceeds the performance goal of 86%.

Primary analyses used the intent to treat (ITT) population. The ITT population was defined as patients who met enrollment criteria, provided signed informed consent, and who had an attempted implant of the LP.

3.4 Patient Follow-up

The primary analysis cohort of 300 patients completed 6-month follow-up in June 2015, triggering the pre-specified primary analysis. At the time of the cutoff, the total cohort of 526 patients had a mean follow-up of 6.9 ± 4.2 months.

3.5 Baseline Demographics and Characteristics

Table 3-1 and **Table 3-2** summarize the demographic and baseline characteristics for the primary analysis cohort as well as the total cohort.

In summary, the average age of patients in the Leadless II study was approximately 76 years and 61.8% were male, which is comparable to other pacemaker studies. Pacemaker indications were atrial fibrillation with atrioventricular block in approximately 56% of patients, sinus rhythm with high-grade atrioventricular block in approximately 9%, and sinus bradycardia with infrequent pauses or syncope in 35%.

Table 3-1: Demographic Information

Demographic Variable	Primary Analysis Cohort (N=300)	Total Cohort (N=526)
Age (years)		
Mean ± Standard deviation (Min, Max)	75.7 ± 11.6 (30.3, 96.7)	75.8 ± 12.1 (19.1, 96.8)
Gender, n (%)		
Male	193 (64.3%)	325 (61.8%)
Female	107 (35.7%)	201 (38.2%)
BMI (kg/m²)		
Mean ± Standard deviation (Min, Max)	29.2 ± 7.3 (15.8, 60.3)	28.7 ± 6.8 (15.2, 60.3)
Race		
American Indian /Alaska Native	1 (0.3%)	1 (0.2%)
Asian	7 (2.3%)	10 (1.9%)
Black/African American	21 (7.0%)	35 (6.7%)
White	269 (89.7%)	478 (90.9%)
Other (Not Specified)	2 (0.7%)	2 (0.4%)
Ethnicity		
Hispanic or Latino	13 (4.3%)	17 (3.2%)
Non-Hispanic or Latino	287 (95.7%)	508 (96.6%)
Other (Not Specified)	0 (0%)	1 (0.2%)

Table 3-2: Medical History Information

Medical History Variable	Primary Analysis Cohort (N=300)	Total Cohort (N=526)
Left Ventricular Ejection Fraction (%)		
Mean ± Standard deviation (n) (Min, Max)	57.1 ± 8.2 (273) (25.0, 80.0)	57.6 ± 8.1 (473) (25.0, 80.0)
Pacemaker Indication		
Chronic AF w/ 2nd or 3rd degree AV block	171 (57.0%)	293 (55.7%)
Sinus rhythm with 2nd or 3rd degree AV block and a low level of physical activity or short expected lifespan	27 (9.0%)	48 (9.1%)
Sinus bradycardia with infrequent pauses or unexplained syncope with electrophysiology findings	102 (34.0%)	185 (35.2%)
Congestive Heart Failure	43 (14.3%)	82 (15.6%)
Class I	11 (3.7%)	18 (3.4%)
Class II	20 (6.7%)	36 (6.8%)
Class III	3 (1.0%)	9 (1.7%)
Class IV	0	0
Unknown	9 (3.0%)	19 (3.6%)
Hypertension	252 (84.0%)	420 (79.8%)
Diabetes	82 (27.3%)	143 (27.2%)
Hyperlipidemia	208 (69.3%)	355 (67.5%)
Coronary Artery Disease	121 (40.3%)	201 (38.2%)
History of Myocardial Infarction	42 (14.0%)	73 (13.9%)
Peripheral vascular disease	45 (15.0%)	69 (13.1%)
History of percutaneous coronary intervention	47 (15.7%)	86 (16.3%)
History of coronary-artery bypass grafting	48 (16.0%)	84 (16.0%)
Tricuspid Valve Disease		
Insufficiency/Prolapse/Regurgitation	60 (20.0%)	109 (20.7%)
Repair/Replacement	3 (1.0%)	3 (0.6%)
Stenosis	0 (0%)	0 (0%)

Medical History Variable	Primary Analysis Cohort (N=300)	Total Cohort (N=526)
Arrhythmia History		
Ventricular (non-sustained)	15 (5.0%)	28 (5.3%)
Supraventricular	231 (77.0%)	399 (75.9%)
Medications		
Antiarrhythmics (Class I or Class III)	28 (9.3%)	48 (9.1%)
Anticoagulants	180 (60.0%)	310 (58.9%)
Antiplatelets	143 (47.7%)	247 (47.0%)
Angiotensin-converting-enzyme Inhibitors	80 (26.7%)	149 (28.3%)
Angiotensin receptor blockers	62 (20.7%)	91 (17.3%)
Beta blockers	120 (40.0%)	199 (37.8%)

3.6 Procedure Characteristics

A Nanostim LP was successfully implanted in 289 of the 300 (96.3%) patients in the primary analysis cohort. As described in the protocol, all eleven (11) patients in whom implant attempts were unsuccessful were withdrawn from the study at 30 days.

Of the 526 patients in the total cohort, a Nanostim LP was successfully implanted in 504 patients (95.8%). The implant procedure was unsuccessful in 21 patients, and in one additional patient the implantation procedure was not attempted since the patient converted to sinus rhythm in the electrophysiology lab and the physician made the decision to place a dual chamber transvenous system. The mean duration of hospital stay from implantation to discharge was 1.1 ± 1.0 days.

Procedure characteristics for those patients with the Nanostim LP successfully implanted are provided in **Table 3-3**. Note that, based on early clinical experience, septal implantation was recommended where possible, leading to a difference in placement location proportions between the primary analysis cohort and total cohort.

Table 3-3: Procedural Characteristics

Procedural Characteristic	Primary Analysis Cohort (N=289)	Total Cohort (N=504)
Duration of implantation (minutes)		
Total: sheath insertion to removal	50.0 ± 27.3	46.5 ± 25.3
Procedure: insertion of delivery catheter to removal	30.4 ± 18.23	28.6 ± 17.8
Duration of fluoroscopy (minutes)	14.9 ± 9.4	13.9 ± 9.1
Device repositioning		
None	199 (68.9%)	354 (70.2%)
1	53 (18.3%)	89 (17.7%)
2	24 (8.3%)	39 (7.7%)
>2	13 (4.5%)	22 (4.4%)
Final device position in right ventricle		
Septal	149 (51.6%)	306 (60.7%)
Apical	140 (48.4%)	192 (38.1%)
Other	0	6 (1.2%)

3.7 Study Outcomes

3.7.1 Primary Effectiveness Endpoints

Of the 300 patients in the ITT population, 270 patients (90.0%) met success criteria for the primary effectiveness endpoint (95% CI: 86.0% to 93.2%). Of these 300 patients, device placement was unsuccessful in 11 patients, and 19 patients did not meet the success criteria. Within the population of patients in the primary analysis cohort who had a successful implant, 270 of 289 patients met success criteria for the primary effectiveness endpoint, or 93.4% (95% CI: 89.9% to 96.0%). **Figure 3-1** presents the success rates for the two analyses and the 95% CI. The lower bound of the 95% CI for success rate exceeds the performance goal of 85%. These data support the conclusion that the primary effectiveness endpoint is met.

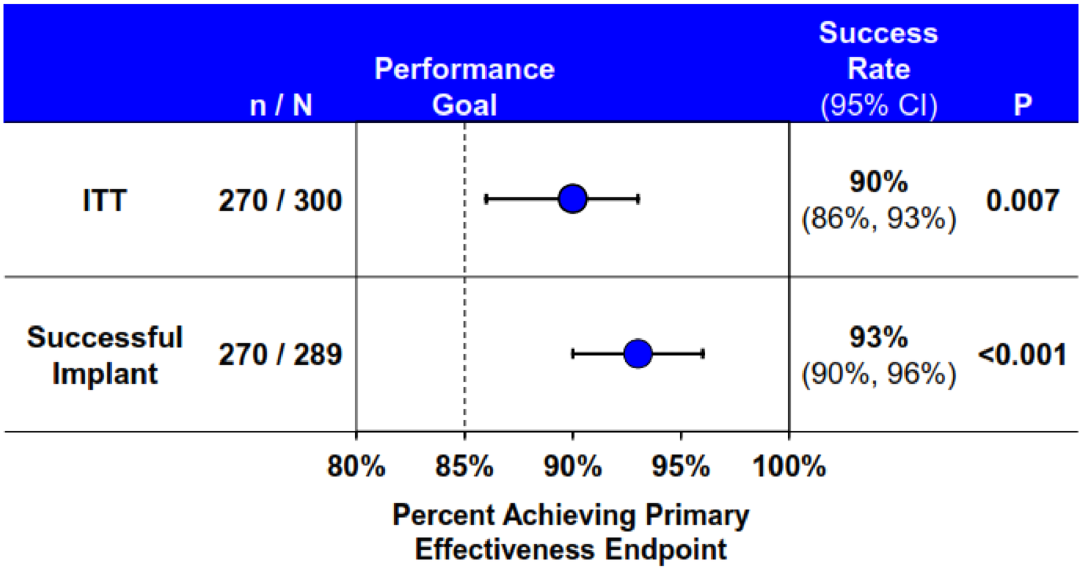


Figure 3-1: Primary Effectiveness Endpoint

Table 3-4 summarizes the reasons for failure of the primary effectiveness endpoint in those patients who had a successful implant. The majority of failures (15) were due to R-wave amplitude at 6 months < 5 mV and < value at implant; none of these patients required an intervention. In another 3 patients, failure was due to pacing threshold > 2 V at 0.4 msec; all 3 patients received a transvenous pacemaker prior to 6 months. One (1) patient did not meet the effectiveness endpoint criteria for both pacing threshold and R-wave amplitude. This patient had high capture threshold and low sensing amplitude at the time of implant and during follow-up. No invasive intervention was required and the patient continues to be followed in the study.

Table 3-4: Reasons for Failure of Primary Effectiveness Endpoint in Patients with Successful Implant

Reason for Failure	Number of Patients
Pacing threshold	4
R-wave amplitude	16
Total	19*

*One patient failed both pacing threshold and R-wave amplitude criteria

3.7.1.1 Pacemaker Performance in Total Cohort

In the total cohort, mean sensing and pacing threshold values improved over time from the values observed at the time of Nanostim LP implantation, as shown in **Figure 3-2** and **Figure**

3-3. Lead impedance decreased over time, and the percent pacing was 38.7 ± 36.9 before hospital discharge and 51.6 ± 39.1 at 12 months (see **Figure 3-4** and **Figure 3-5**).

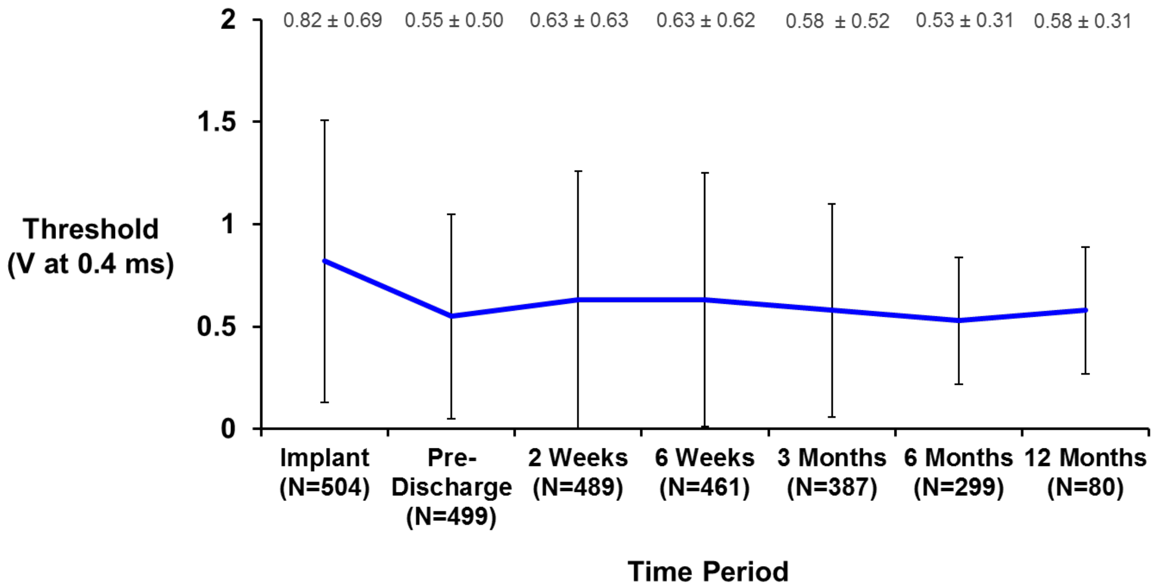


Figure 3-2: Pacing threshold over time for Total Cohort

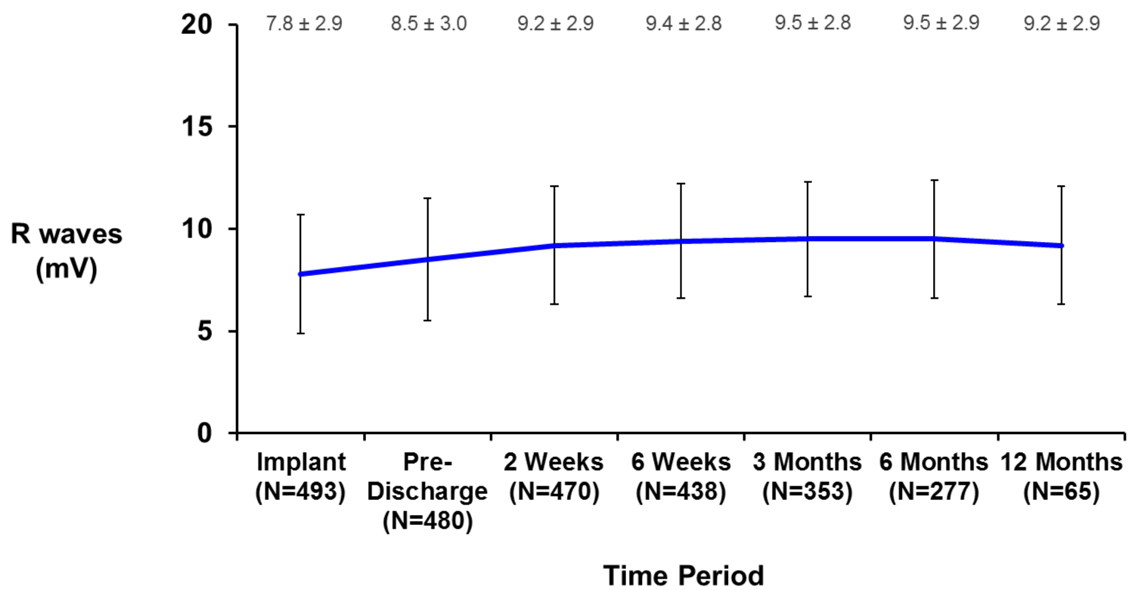


Figure 3-3: Sensed R-waves over time for Total Cohort

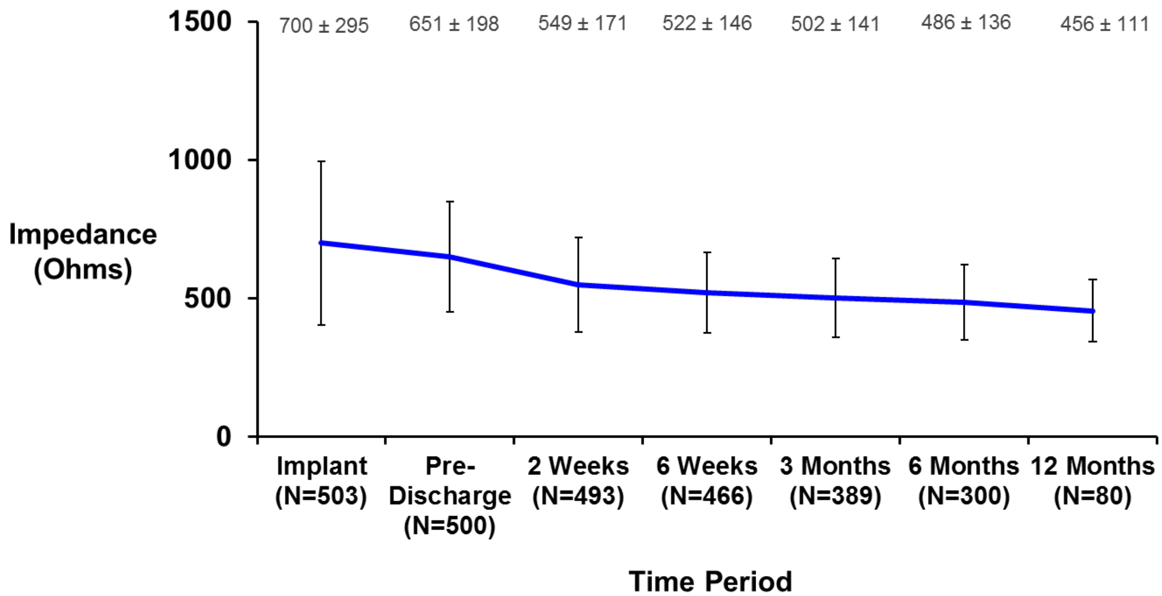


Figure 3-4: Impedance over time for Total Cohort

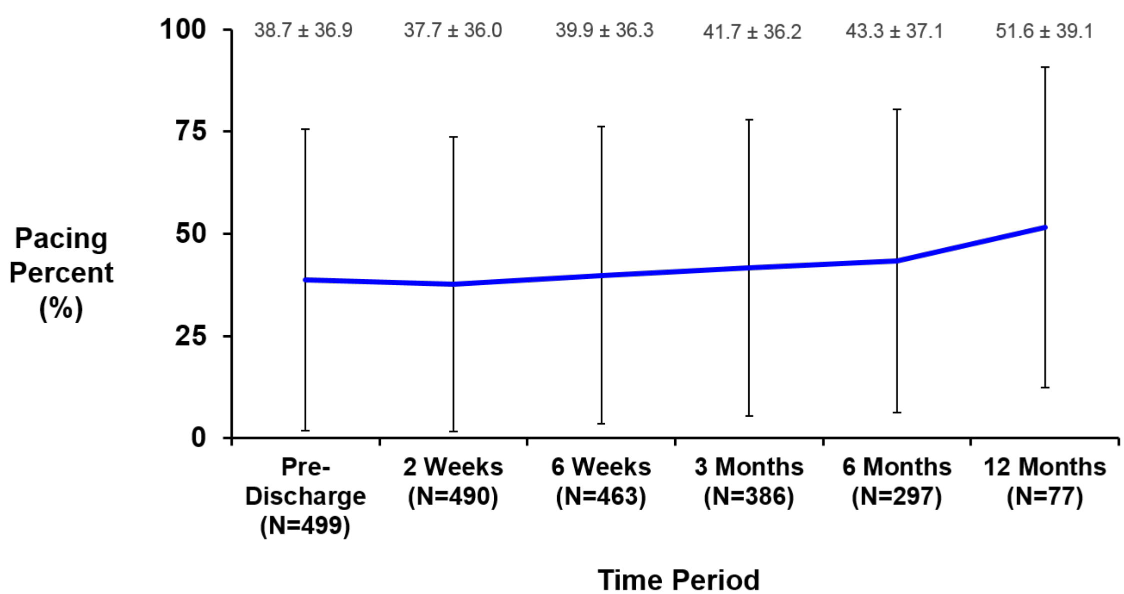


Figure 3-5: Pacing Percent over time for Total Cohort

Battery longevity estimates over a range of pacing percentages are shown in **Table 3-5** and based on assumptions of VVIR pacing at 60 bpm and output 2.5 V at 0.4 msec. In accordance with ISO 14708-2:2012, mean battery longevity has been estimated to be 15.0 ± 6.7 years (95% CI, 14.2 to 15.8) which is based on observed device-use conditions of the primary analysis cohort through 6 months.

Table 3-5: Estimated Battery Longevity

	Battery Longevity (Years)	
Percent Pacing	**500 Ohm Load**	**600 Ohm Load**
100	8.3	9.3
75	10.0	11.0
50	12.6	13.7
25	17.0	17.9

3.7.2 Primary Safety Endpoint

Among 300 patients in the primary analysis cohort, 20 patients experienced 22 complications (i.e. SADEs as adjudicated by the CEC). The remaining 280 patients (93.3%) met the success criteria for the primary safety endpoint. **Figure 3-6** presents the estimated complication free rate along with the 95% CI. The 95% CI for CFR is (89.9%, 95.9%), the lower bound of which exceeds the performance goal of 86%. Hence, the null hypothesis is rejected at the 2.5% significance level, and it is concluded that the primary safety endpoint is met.

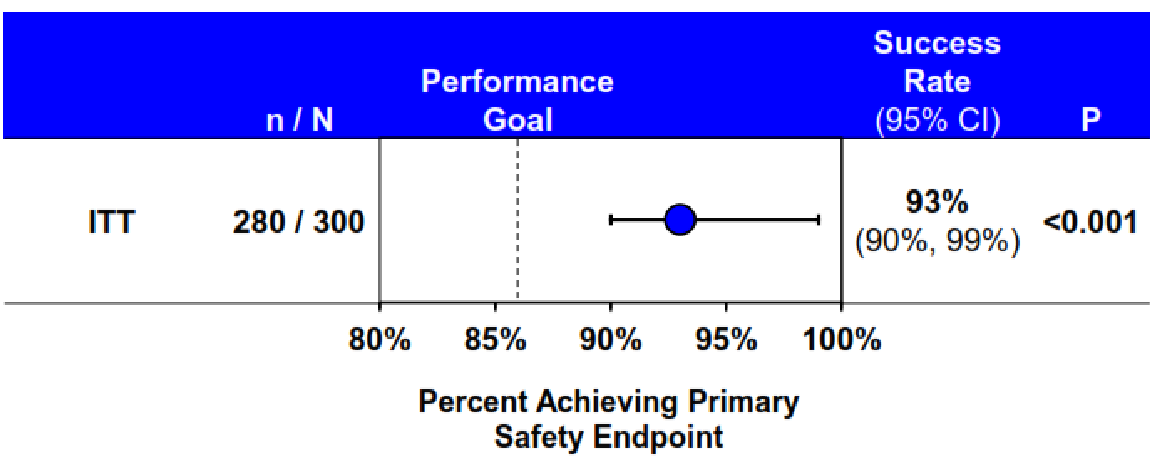
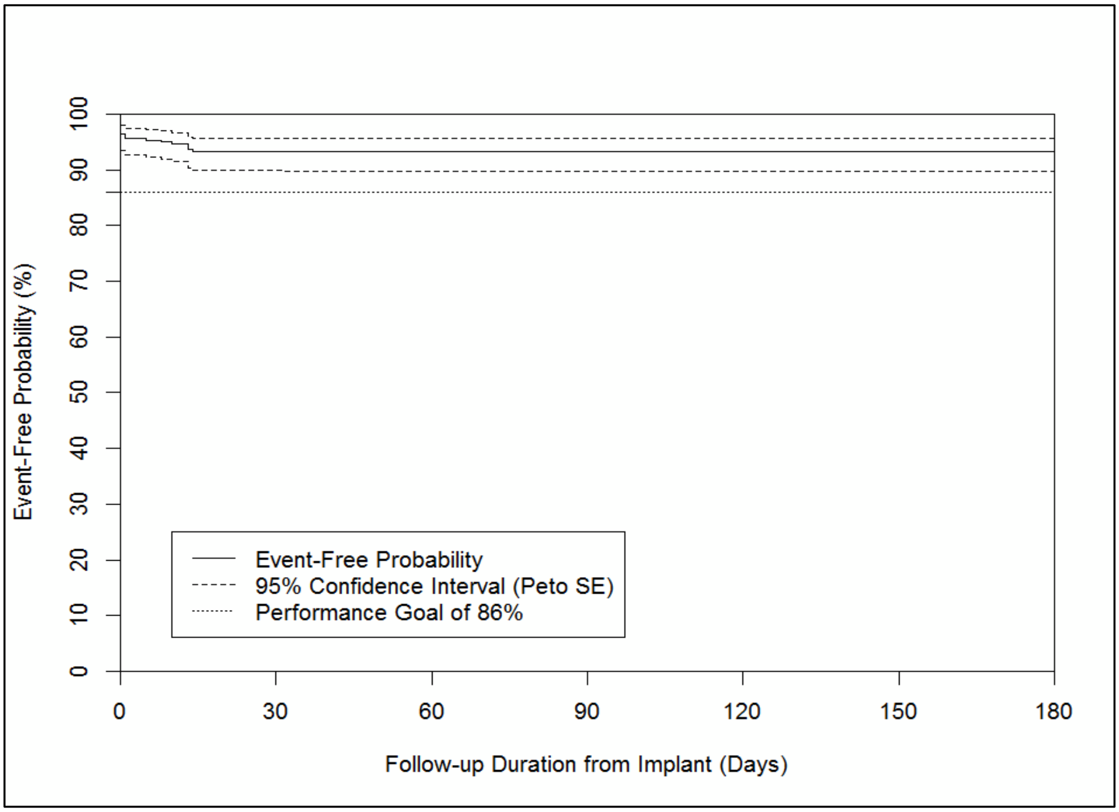


Figure 3-6: Primary Safety Endpoint

Figure 3-7 shows the Kaplan-Meier estimate of freedom from SADEs in the primary cohort. The majority of these events were noted in the first two weeks post-implantation and none occurred after the early post-procedure period.

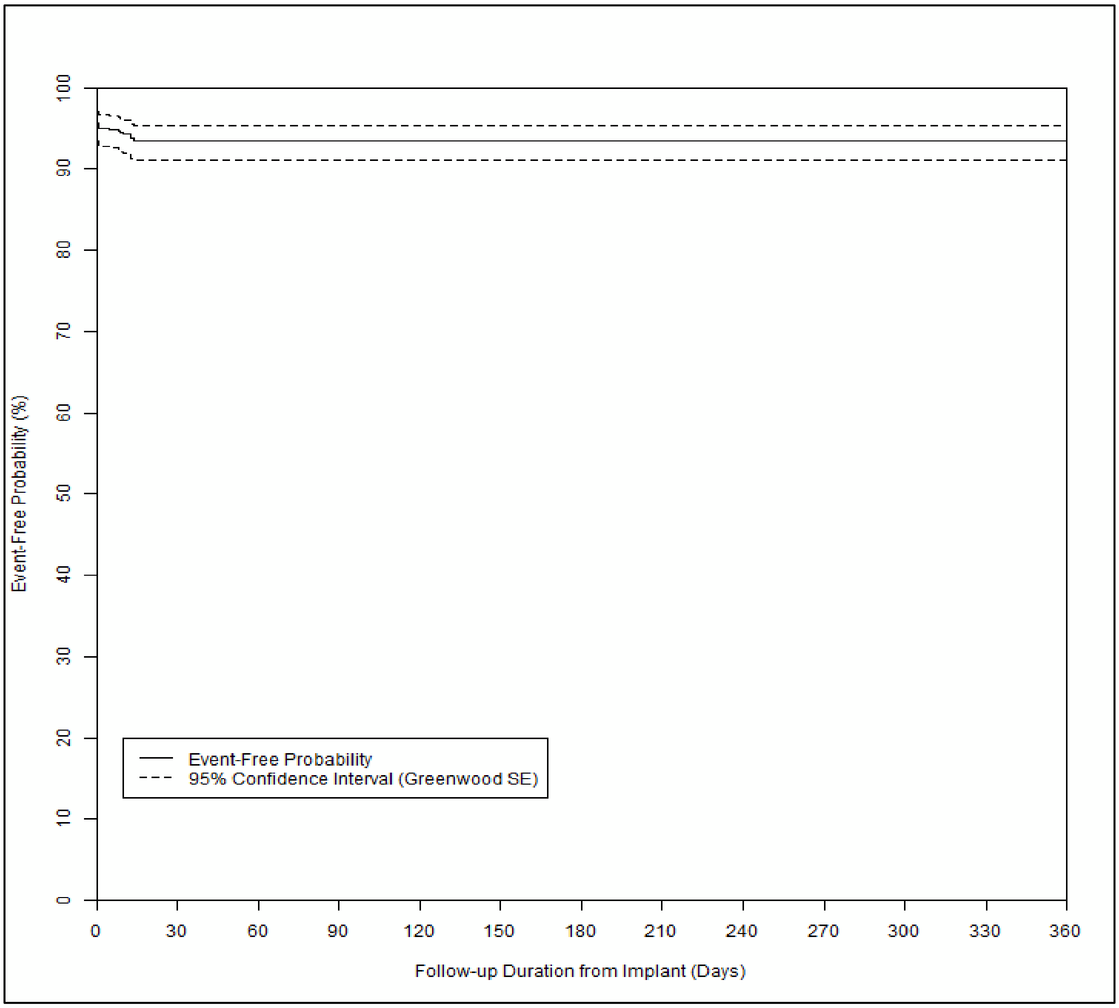


Data Category	Follow-up Duration from Implant (Days)						
	0	**30**	**60**	**90**	**120**	**150**	**180**
At Risk	300	278	267	265	264	263	262
Event	11	20	20	20	20	20	20
Survival	96.3%	93.3%	93.3%	93.3%	93.3%	93.3%	93.3%
95% CI	(93.5%, 97.9%)	(89.8%, 95.6%)	89.8%, 95.7%)	(89.7%, 95.7%)	(89.7% 95.7%)	(89.7%, 95.7%)	(89.7%, 95.7%)

Figure 3-7: Kaplan-Meier Analysis of Primary Safety Endpoint (N=300)

3.7.2.1 Primary Safety Endpoint in Total Cohort

The complication free rate was also assessed for the total cohort of 526 enrolled patients. **Figure 3-8** shows a Kaplan-Meier analysis for freedom from complications through 12 months on the total cohort. The Kaplan-Meier analysis shows that the 6-month CFR estimate is consistent with the estimate obtained in the primary ITT analysis; the lower bound of the 95% CI is 91.1%, greater than the performance goal of 86% set for the primary safety endpoint. As with the primary analysis cohort of 300 patients, all SADEs occurred within the early peri-procedural period and no late SADEs occurred in this total cohort.



Data Category	Follow-up Duration from Implant (Days)							
	0	**30**	**60**	**90**	**120**	**150**	**180**	**360**
At Risk	526	479	430	381	334	308	279	70
Event	23	34	34	34	34	34	34	34
Survival	95.6%	93.5%	93.5%	93.5%	93.5%	93.5%	93.5%	93.5%
95% CI	(93.5%, 97.1%)	(91.1%, 95.3%)	(91.1%, 95.3%)	(91.1%, 95.3%)	(91.1%, 95.3%)	(91.1%, 95.3%)	(91.1%, 95.3%)	(91.1%, 95.3%)

Figure 3-8: Kaplan-Meier Analysis of Freedom from SADEs for the Total Cohort

Table 3-6 summarizes the SADEs for the primary analysis cohort and the total cohort. In the total cohort, the rate of SADEs was 6.5%. Cardiac perforation was reported in 1.5% (8/526) of patients and included two patients with reported pericardial effusion with no intervention. Device dislodgement was noted in 1.1% (6/526) of patients. The six dislodgements were identified at 8.0 ± 6.4 days after implantation (range of 1 to 14 days). In these patients, device migration to the pulmonary artery occurred in 4 patients, and in the remaining 2 patients the device migrated to the right femoral vein. In each case the device was retrieved percutaneously. In 0.8% (4/526) of patients the device required replacement due to elevated pacing thresholds; in each case retrieval and replacement were performed successfully.

Table 3-6: Serious Adverse Device Effects

	Primary Analysis Cohort (N = 300)			Total Cohort (N = 526)		
	Events	Patients with Events		Events	Patients with Events	
Event Description	**(N)**	**(N)**	**(%)**	**(N)**	**(N)**	**(%)**
Total	**22**	**20***	**6.7%**	**40**	**34***	**6.5%**
Cardiac Perforation						
Cardiac tamponade with intervention	1	1	0.3%	5	5	1.0%
Cardiac perforation requiring intervention	1	1	0.3%	1	1	0.2%
Pericardial effusion with no intervention	2	2	0.7%	2	2	0.4%
Vascular complication						
Bleeding	2	2	0.7%	2	2	0.4%
Arteriovenous fistula	1	1	0.3%	1	1	0.2%
Pseudoaneurysm	1	1	0.3%	2	2	0.4%
Failure of vascular closure device requiring intervention	0	0	0	1	1	0.2%
Arrhythmia during device implantation						
Asystole	1	1	0.3%	1	1	0.2%
Ventricular tachycardia or ventricular fibrillation	1	1	0.3%	2	2	0.4%
Cardiopulmonary arrest during implantation procedure	0	0	0	1	1	0.2%
Device dislodgement	5	5	1.7%	6	6	1.1%
Device migration during implantation owing to inadequate fixation	0	0	0	2	2	0.4%
Pacing threshold elevation with retrieval and implantation of a new device	4	4	1.3%	4	4	0.8%

Event Description	Primary Analysis Cohort (N = 300)			Total Cohort (N = 526)		
	Events (N)	Patients with Events (N)	Patients with Events (%)	Events (N)	Patients with Events (N)	Patients with Events (%)
Other						
Hemothorax**	0	0	0	1	1	0.2%
Angina pectoris	0	0	0	1	1	0.2%
Pericarditis	1	1	0.3%	1	1	0.2%
Acute confusion and expressive aphasia	0	0	0	1	1	0.2%
Dysarthria and lethargy after implantation	0	0	0	1	1	0.2%
Contrast-induced nephropathy	0	0	0	1	1	0.2%
Orthostatic hypotension with weakness	1	1	0.3%	1	1	0.2%
Left-leg weakness during implantation	0	0	0	1	1	0.2%
Hospitalization for chest pain due to presumed pulmonary embolism	1	1	0.3%	1	1	0.2%
Ischemic stroke	0	0	0	1	1	0.2%

* Some patients experienced more than one event - therefore the number of patients is less than the number of events

** The hemothorax is related to the cardiac tamponade that required intervention and resulted in hemodynamic compromise requiring CPR. As a result of chest compressions and high pressure within the pericardium due to tamponade, it was believed that the hemothorax was a direct consequence of LP procedure. The CEC adjudicated this event as related to implant procedure and not device related.

3.7.2.2 Interpretation of SADE Findings

Findings from the Leadless II study can be put into context by comparing to outcomes of conventional pacemaker studies. One such study described in the literature is the FOLLOWPACE study, conducted among 1517 patients in the Netherlands who received a pacemaker.[14] Because of differences in study design, data collection, and conduct, a direct comparison of safety outcomes has limitations, but the rates of different adverse events are useful for noting similarities and differences in the safety profiles of the Nanostim LP and conventional pacemakers. Demographics and characteristics of the patient populations from the two studies are shown in **Table 3-7**. Age, gender, and BMI were similar between the studies' cohorts. The Leadless II total cohort has higher comorbidity rates, but the key difference is the type of pacemaker used. The FOLLOWPACE study included single- and dual-chamber pacemakers.

Table 3-7: Patient Demographics and Characteristics from Leadless II and FOLLOWPACE Studies

Demographic/Characteristic	Leadless II Total Cohort (N=526)	FOLLOWPACE Cohort (N=1517)
Age (years)		
Mean ± Standard deviation	75.8 ± 12.1	73.7 ± 10.8
Gender (%)		
Male	61.8%	56.4%
BMI (kg/m²)		
Mean ± Standard deviation	28.7 ± 6.8	26.3 ± 3.7
Medical History (%)		
Coronary artery disease	38.2%	19.8%
Hypertension	79.8%	62.8%
Diabetes Mellitus	27.3%	15.2%
Use of anticoagulants	58.9%	62.1%
Pacemaker Type (%)		
Single-chamber system AAIR	0%	1.5%
Single-chamber system VVIR	100%	25.1%
Dual-chamber system	0%	73.3%

The mean follow-up duration in the Leadless II IDE for the total cohort is 6.9 ± 4.2 months while that in the FOLLOWACE study is 5.8 ± 1.1 years. The safety data for the FOLLOWPACE study are divided into those events that occurred in first 2 months and those that were detected after 2 months. The cardiac perforation/pericardial effusion rate in the Leadless II IDE study is higher than that observed in right ventricular (RV) leads in the FOLLOWPACE study in the first 2 months. On the other hand, dislodgements, vascular complications and pneumothorax/ hemothorax were higher in the FOLLOWPACE study in the first 2 months as compared to those in the LEADLESS II IDE study. Additionally, infections, lead related complications and pocket complications observed in the FOLLOWPACE study in the first 2 months added up to 6.3% and are non-existent in the LEADLESS II IDE study. Finally, there were 3.9% lead and pocket related complications in the FOLLOWPACE study in the chronic phase which are not expected to occur with a leadless pacemaker due to absence of lead and pocket.

Table 3-8: Key Events from Leadless II and FOLLOWPACE Studies

Serious Adverse Device Effect	% Patients with Event		
	Leadless II Total Cohort (N=526)	FOLLOWPACE Cohort - First 2 months (N=1517)	FOLLOWPACE Cohort - After 2 months (N=1517)
Cardiac Perforation/Pericardial Effusion	1.5%	0.3%	0.1%
Device Dislodgement	1.1%	1.6%	0.7%
Pacing Threshold Elevation	0.8%	0.8%	1.7%
Vascular Access Related Complications	1.1%	5.4%	0.2%
Pneumothorax/Hemothorax	0.2%	2.2%	0.0%
Other Lead Related Complications (fracture, insulation, diaphragmatic stimulation)	-	1.5%	2.0%
Pocket Complications	-	3.4%	1.9%
Infection (Pocket/Lead)	-	1.4%	1.5%

Key Finding: While some events were reported more frequently in the Leadless II study, a number of significant complications are eliminated (lead complications as well as pocket complications) due to the design of the Nanostim LP. Overall, the short-term safety profiles demonstrated in the two studies are similar. Long-term data on the Nanostim LP will continue to be gathered.

3.7.2.3 Predictors of Adverse Events

An analysis was conducted to assess which, if any, variables were predictors of adverse events in the Leadless II study. Univariate logistic regression modelling was conducted with the following explanatory variables:

- Age
- BMI
- Sex
- Prior cardiac intervention [coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), stent, atherectomy, or ablation]
- Use of anticoagulants

- Use of antiplatelets
- Whether or not repositioning had been attempted

Results of this analysis are detailed in **Table 3-9** and demonstrate that, at the 5% significance level, there were no significant predictors of having an SADE. A stepwise multivariate model led to the same results, with no significant predictors of having an SADE.

Table 3-9: Assessment of Predictors of SADEs

Variable	Odds Ratio*	95% CI for Odds Ratio	p-value
Age	1.008	0.978, 1.040	0.592
BMI	0.95	0.893, 1.010	0.098
Sex (Male)	0.526	0.262, 1.058	0.072
Prior Cardiac intervention	0.768	0.359, 1.644	0.497
Use of Anticoagulants	0.875	0.434, 1.763	0.708
Use of Antiplatelets	0.683	0.334, 1.394	0.295
Repositioning (Y/N)	1.708	0.840, 3.475	0.139

Based on univariate logistic regression model

Key Finding: In the Leadless II study there were no subgroups of patients identified as having an increased risk for SADEs, at the 5% significance level.

3.7.3 Deaths and Unanticipated Adverse Device Effects

3.7.3.1 Deaths

Twenty-eight (28) of the 526 patients in the total cohort died during follow- up. There were no intra-procedural deaths. The mean age of patients at death was 79.1 ± 10.9 years (range of 40.1 to 96.7). Of the 28 deaths reported in the Total Cohort, 67.9% occurred within 6 months post implant, 28.6% occurred between 6 and 12 months, and 3.6% occurred after 12 months. As shown in **Table 3-10**, cause of death was reported as cardiac related in 4 patients, non-cardiac in 14 patients, and unknown in 10 patients. None of the deaths were considered to be LP related.

Table 3-10: Deaths Classified by CEC Adjudication in Total Cohort

Cause of Death	Number of Patients	Relation to Device or Procedure	Number of Days Post-Implant
Cardiac			
Arrhythmic	2	Not Related (1); Procedure (1)	18, 100
Heart failure	1	Not Related (1)	99
Unknown	1	Procedure/ Introducer (1)	14
Non-cardiac			
Accidental gunshot wound	1	Not Related (1)	47
Renal or liver failure	5	Not Related (5)	73, 82, 89, 135, 320
Respiratory failure	3	Procedure (1) Not Related (2)	10, 103, 182
Multiple organ failure	2	Not Related (2)	34, 38
Ischemic bowel/small bowel obstruction	2	Not Related (2)	185, 270
Mixed respiratory and metabolic acidosis	1	Not Related (1)	176
Unknown*			
Death- Sudden with antecedent worsening heart failure	1	Not Related (1)	267
Death- Sudden without antecedent worsening heart failure	1	Not Related (1)	274
Death- Non-sudden with antecedent worsening heart failure	2	Not Related (2)	18, 42
Death- Non-sudden with antecedent worsening heart failure status unknown	1	Not Related (1)	281
Death-Unknown (presumed sudden) with no antecedent worsening heart failure	3	Not Related (2) Unknown (1)	5, 69, 126
Death-Unknown (presumed sudden) with antecedent worsening heart failure status unknown	1	Not Related (1)	219
Death- Unknown temporal cause and antecedent worsening heart failure status unknown	1	Not Related (1)	409
Total	**28**		

* Sudden death: death ≤1 hour after onset of symptoms
Non-sudden death: death > 1 hour after onset of symptoms
Death Unknown (presumed sudden): documentation of patient's condition by a witness within 24hours
Death Unknown: death where onset of symptoms cannot be determined

Three deaths in the total cohort were classified by the CEC as procedure related (3/526; 0.6%). These deaths occurred within 30 days from the date of the attempted LP implant. The experience of these three patients is described in more detail.

The first patient, a 71 year-old male, had a past medical history of squamous cell carcinoma of the tongue with metastasis to the throat and was under treatment with oral chemotherapeutic agents, post radical neck dissection with lymphadenopathy, and had open sores on the neck from radiation therapy. The patient was admitted to the hospital for syncope and then enrolled in the Leadless II study. During the attempted implant, the patient could not be placed in a supine position due to a constrictive airway. As the device was being advanced into the apical right ventricular septum, the patient became acutely hypoxic and unresponsive. The LP was emergently removed through the sheath and a transvenous pacemaker was placed. Extensive swelling from radiation therapy created difficulty in creating an airway and the patient deteriorated and suffered a cardiopulmonary arrest. Once an airway was established, the patient stabilized. A transthoracic echocardiogram was negative for pericardial effusion, but showed severe hypokinesis of the apex. One week later, the patient required a tracheostomy without complication due to ventilator dependence. The following day, the patient had episodes of bradycardia and hypotension that were treated with fluid challenges and Levophed. Eighteen days after attempted device placement, the patient had a decreased level of consciousness that deteriorated to a cardiopulmonary arrest due to ventricular fibrillation and the patient was pronounced deceased. **CEC Classification**: *Cardiac: Arrhythmic, Temporal course-sudden, related to procedure, unrelated to investigation and retrieval catheter, and unknown relatedness to device and introducer.*

The second patient, an 89 year-old male, underwent successful placement of the Nanostim LP, complicated by a large groin hematoma and a drop in Hemoglobin from 12.4 g/dl to 8.7 g/dl. Following stabilization, the patient was discharged from the hospital. During a clinic visit 6 days post-implant, an ecchymosis was observed. The patient suffered a fatal cardiac arrest related to ventricular fibrillation 14 days post-implant. **CEC Classification**: *Cardiac–unknown, temporal course-unknown (presumed sudden), not related to LP or investigation, but related to procedure and 18 Fr Introducer***.**

The third patient, a 74 year-old female, had tortuous venous anatomy and underwent an unsuccessful LP implant, complicated by a pericardial effusion requiring pericardiocentesis. The patient developed atrial fibrillation with a rapid ventricular response 2 days after the attempted implant. The patient was treated with antiarrhythmic therapy and cardioversion to restore sinus rhythm, and discharged from the hospital in stable condition. The patient presented again two days later with an abrupt onset of mild expressive aphasia and was found to be in atrial fibrillation with rapid ventricular rates. A computed tomography (CT) scan of the brain demonstrated a large left middle cerebral artery infract without hemorrhage transformation and a subsequent CT perfusion angiography demonstrated a perfusion defect in the left middle cerebral artery territory without evidence of an occlusion. The hospital course was complicated by dysphagia requiring an enteral feeding tube and hypercarbic respiratory failure requiring bilevel positive airway pressure (BiPAP). Atrial fibrillation was treated with warfarin and amiodarone and diastolic heart failure was treated with diuretics. During replacement of the enteral feeding tube, the patient developed hypercarbia (pCO_2 130 mmHg, pH 7.11, and oxygen saturation 88%) and hypotension (79/39 mmHg) while not on BiPAP. Despite initial stabilization the clinical status continued to deteriorate. Chest radiography revealed worsening pleural effusions and transthoracic echocardiography showed a small pericardial effusion with moderate pulmonary hypertension (right ventricular systolic pressure 57 mmHg). The patient's status was changed to "Do Not Resuscitate" due to the family's desire to avoid mechanical ventilation. The patient ultimately expired 8 days after the failed LP implant. **CEC Classification:** *Non-Cardiac, Temporal course-Non-sudden, unrelated to investigation, device but related to the procedure***.**

3.7.3.2 Unanticipated Adverse Device Effects

There were no unanticipated adverse device effects reported over the course of the study.

3.7.4 Non-Device-Related Serious Adverse Events

Non-device-related serious adverse events, as assessed by the CEC, were reported in 6.3% of the primary cohort, and 5.5% of the total cohort. **Table 3-11** includes the full listing of these events for the primary analysis cohort and total cohort.

Table 3-11: Non-Device-Related Serious Adverse Events

	Primary Analysis Cohort (N = 300)			Total Cohort (N = 526)		
	Events	Patients with Events		Events	Patients with Events	
Event Description	**(N)**	**(N)**	**(%)**	**(N)**	**(N)**	**(%)**
Total	**22**	**19***	**6.3%**	**36**	**29***	**5.5%**
Acute renal failure	1	1	0.3%	2	2	0.4%
Angina pectoris	1	1	0.3%	2	2	0.4%
Atrial fibrillation with rapid ventricular rates	1	1	0.3%	1	1	0.2%
Bacteremia	0	0	0	1	1	0.2%
Bell's palsy	1	1	0.3%	1	1	0.2%
Bilateral pulmonary emboli with pulmonary infarction	1	1	0.3%	1	1	0.2%

Event Description	Primary Analysis Cohort (N = 300)			Total Cohort (N = 526)		
	Events (N)	Patients with Events (N)	Patients with Events (%)	Events (N)	Patients with Events (N)	Patients with Events (%)
Change in mental status	1	1	0.3%	1	1	0.2%
Dizziness	2	2	0.7%	3	2	0.4%
Heart failure	0	0	0	4	4	0.8%
Heart failure and gout	1	1	0.3%	1	1	0.2%
Hypertensive emergency	1	1	0.3%	1	1	0.2%
Lung cancer	1	1	0.3%	1	1	0.2%
Mechanical fall	0	0	0	1	1	0.2%
Methicillin-resistant *Staphylococcus aureus* infection	1	1	0.3%	1	1	0.2%
Myocardial infarction	1	1	0.3%	1	1	0.2%
Palpitations	1	1	0.3%	1	1	0.2%
Pericardial effusion after placement of epicardial lead	1	1	0.3%	1	1	0.2%
Reduction in ejection fraction: new onset	0	0	0	1	1	0.2%
Seizure: new onset	0	0	0	1	1	0.2%
Sepsis	2	2	0.7%	2	2	0.4%
Shortness of breath	1	1	0.3%	1	1	0.2%
Stroke	1	1	0.3%	1	1	0.2%
Syncope: unknown cause	1	1	0.3%	1	1	0.2%
Syncope: vasovagal	1	1	0.3%	1	1	0.2%
Urinary retention	1	1	0.3%	1	1	0.2%
Ventricular tachycardia or ventricular fibrillation	0	0	0	2	2	0.4%
Vertigo	0	0	0	1	1	0.2%

*Some patients experienced more than one event – therefore the number of patients is less than the number of events

3.7.5 Device Retrieval

A key feature of the Nanostim LP is that it is designed to be retrievable. Demonstration of this feature was noted in the Leadless II study. In addition to the 6 patients in the total cohort who required device retrieval following dislodgements, there were 7 patients who underwent successful retrieval of the Nanostim LP from the implant site without complications. These patients are listed in **Table 3-12**. Retrieval took place at an average of 160 ± 180 days post-implant (median, 100 days; range 1 to 413 days). The reasons for retrieval were elevated pacing thresholds in 4 patients, worsening heart failure requiring CRT in 2 patients, and elective explantation in 1 patient who decided he no longer wanted a foreign object in his body. Three (3) patients received new leadless cardiac pacemakers, 2 received conventional pacemakers, and the 2 patients with heart failure received cardiac-resynchronization therapy with either direct His-bundle pacing or biventricular pacing.

Table 3-12: Patients Undergoing Device Retrieval

Patient	Duration of implant (days)	Reason for retrieval	Replacement option
1	1	Elevated pacing thresholds	Nanostim LP
2	1	Elevated pacing thresholds	Nanostim LP
3	100	Elevated pacing thresholds	Nanostim LP
4	13	Elevated pacing thresholds	Conventional pacemaker
5	208	Worsening heart failure	CRT
6	413	Worsening heart failure	CRT
7	382	Elective explantation	Conventional pacemaker

3.8 Additional Clinical Data

In addition to data from the Leadless II study, there are two studies conducted in Europe. The first was a pre-market study to support the initial CE-mark. The second, the Leadless Observational Study is a larger post-market clinical follow-up (PMCF) registry conducted to fulfill the post-market commitments.

The pre-CE mark clinical investigation was a prospective, non-randomized, single-arm, multicenter clinical investigation. This clinical investigation evaluated the safety and performance of the Nanostim LP in 30 patients for the treatment of bradycardia. The primary study objective, complication-free rate through 3 months, was met and confirmed that the devices performed as intended in the clinical context. Data through 12 months show that the Nanostim LP had stable performance and reassuring safety outcomes. The majority of complications were acute and occurred in the first month following the implant. The study also demonstrated appropriate pacing and sensing, measured by pacing thresholds, R-wave amplitudes, pacing impedances.[28]

The EU registry, the Leadless Observational Study, is ongoing in Europe. The study is a 5-year prospective study and will include up to 1000 patients. The primary endpoint is the 180-day SADE-free rate. Data from this study (300 patients with 6 months of follow-up) are being used towards meeting the post-market regulatory commitments for CE marking.

During the course of this PMCF study, St. Jude Medical became aware of two separate myocardial perforations that led to patient death. As a result, St. Jude Medical voluntarily and temporarily paused new implants to perform a thorough analysis and investigation of the events. The investigation revealed that these two specific cases involved patients with particularly challenging clinical presentations (e.g., recent previous surgery, short life expectancy) that increased the risks associated with pacemaker implantation. Broadly, there were a number of learnings from the early EU registry experience. Several corrective actions were implemented, including:

- Additional physician training which involved review of video compendium highlighting the best and worst case implantation scenarios
- Alignment of the registry study protocol with the Leadless II IDE protocol, particularly with regard to the patient exclusion criteria. In some cases, Nanostim was initially being used as a device of last resort in patients who were not eligible for conventional pacemakers.
- Instructions for Use were updated, including addition of specific warnings and emphasis of key implantation steps:
    - All perforations were associated with RV apical implants. This led to the recommendation that whenever possible, devices be placed in the lower septum.
    - Quick rotation may cause the catheter to over-rotate due to torque buildup. This led to the recommendation that the catheter be rotated slowly with pauses for 1 – 1.25 turns.
    - In order to avoid too much pressure on the endocardium, the recommendation was revised such that the protective sleeve is to be pulled back before engaging the endocardium
    - In order to avoid unnecessary repositioning attempts, the importance of waiting for up to 20 minutes after initial implant was emphasized, in order for current of injury to resolve before deciding whether repositioning is necessary.
    - Presence of an existing perforation was observed in at least one case leading to addition of an IFU warning to not implant the device in presence of an existing perforation.

- Suboptimal imaging equipment contributed to at least one cardiac perforation so all sites were then required to use high resolution fluoroscopy equipment during implant.

No device or delivery system changes were made. The corrective actions implemented resulted in a reduction of the overall perforation rate. The rate dropped from 4.1% in the pre-pause cohort to 2.2% in the post-pause cohort (representing a 50% reduction). The dislodgement rate also decreased, from 1.4% to 0.0%. The overall complication rate was reduced from 8.6% pre-pause to 6.5% post-pause (data based on a cutoff date of January 9, 2015. This considerable reduction confirms that the corrective actions implemented in the EU registry positively impacted outcomes. **Table 3-13** below provides the rates of serious adverse device effects associated with EU registry before and after the corrective actions, as well the Leadless II rates for those events.

Table 3-13: SADEs in EU Registry (pre-pause), EU Registry (post-pause) and Leadless II Study

Serious Adverse Device Effect – Complications	EU Registry – Pre-Pause (N=147)	EU Registry – Post-Pause (N=93)	Leadless II study Implants (N=526)
Pericardial Effusion or Perforation	4.1%	2.2%	1.5%
Dislodgement	1.4%	0.0%	1.1%
Intermittent capture, failure to capture, or elevated threshold	0.0%	1.1%	0.8%
Device migration during implantation owing to inadequate fixation	0.7%	0.0%	0.4%
Vascular Complication	0.7%	0.0%	1.1%
Infection	0.0%	0.0%	0.0%

EU registry data based on data through January 9, 2015; Leadless II data based on available data through June 29, 2015.

4. Post-Approval Study Proposal

In order to gather further long-term safety data on the Nanostim LP, St. Jude Medical is proposing to conduct a 7-year, 1700 patient post-approval study (PAS), the Nanostim Leadless PAS. Data collected will help to characterize acute and long term safety, as well as patient management when the device needs to be replaced or deactivated. The study design has been revised from the proposal submitted to FDA, based on Agency feedback and may be further modified following the panel discussion.

The PAS will gather data on acute and long-term performance of the Nanostim LP, with a sample size that allows for estimation of adverse event rates to within a 1% confidence interval width. All adverse events reported in the study will be included in periodic study reports. Patient and device management when the Nanostim LP is indicated for replacement or deactivation will be studied as well.

4.1 PAS Study Design

The proposed PAS is a prospective, non-randomized, multi-center clinical study designed to evaluate the long-term safety of the Nanostim™ Leadless Pacemaker in patients with a VVIR pacing indication.

4.2 PAS Inclusion and Exclusion Criteria

4.2.1 PAS Inclusion Criteria

In order to participate in the study, patients must meet all of the following inclusion criteria:

- Have an approved indication per ACC/AHA/HRS/ESC guidelines for implantation of a VVIR pacemaker
- Patients meets at least one of the following criteria:
  - Is a Leadless II study patient who is being rolled over into the Leadless PAS
  - Is a patient who will be implanted with a Nanostim LP
- Patient is at least 18 years of age or above, or of legal age to give informed consent specific to state and national law
- Patient is capable of signing an IRB approved informed consent (Legal Guardian is not acceptable)
- Patient is willing to comply with the prescribed follow-up tests and schedule of evaluations.

4.2.2 PAS Exclusion Criteria

Patients meeting any of the following exclusion criteria are not eligible for study participation:

Group A: For Leadless II study patients who are being rolled over into the Leadless PAS

- Patient has been enrolled or intends to participate in a clinical drug and/or device study, which could confound the results of this trial as determined by SJM, during the course of this PAS

Group B: For patients who will be implanted with a Nanostim LP

- Patient has known pacemaker syndrome, has retrograde ventriculoatrial conduction, or suffers a drop in arterial blood pressure with the onset of ventricular pacing
- Patient has a life expectancy of less than 5 years due to any condition
- Patient is allergic or hypersensitive to DSP
- Patient has a mechanical tricuspid valve prosthesis
- Patient has a pre-existing endocardial pacing or defibrillation leads
- Patient has current implantation of either conventional or subcutaneous ICD or CRT device
- Patient has an implanted inferior vena cava filter
- Patient has evidence of thrombosis in one of the veins used for vascular access during the procedure
- Patient has been enrolled or intends to participate in a clinical drug and/or device study, which could confound the results of this trial as determined by SJM, during the course of this PAS
- Patient had cardiovascular or peripheral vascular surgery within 30 days of implant*

4.3 PAS Study Procedures

Patients will be considered enrolled in the study on the date that they sign the IRB approved informed consent. New patients who meet the inclusion and exclusion criteria, sign the informed consent form, and have an implanted or attempted implant on the Nanostim LP will be considered enrolled in the study.

Patients will be seen on the day of implantation, pre-discharge, 2 weeks post-implant, 6-months post-implant, and then every 6-months through 7-years post-implant. Procedure and data collection throughout the study is shown in **Table 4-1** and **Table 4-2**. The Investigation team will:

- Assess for Adverse Device Effects (ADEs), Serious Adverse Device Effects (SADEs), complications and deviations from protocol
- Measure and record the following device parameters:
    - Capture threshold
    - Pacing Impedance
    - R-wave amplitude
    - Battery voltage and estimated recommended replacement time

If the patient has the Nanostim LP removed or deactivated at any time during the study, the reason for deactivation or removal (end of life, device upgrade, elective explant, other) will be documented, including the following information:

- Remaining longevity of currently implanted LP (if not at end of life)
- Treatment of patient following removal or deactivation of LP:
    - Whether the LP was explanted and another LP was implanted
    - Whether the LP was explanted and a pacing or defibrillation lead was implanted
    - Whether the LP was disabled and another LP was implanted adjacent to the existing LP
    - Whether the LP was disabled and a pacing or defibrillation lead was implanted adjacent to the existing LP
    - Other

The patient will be followed for 30 days following removal or deactivation to document adverse events and withdrawn thereafter from the study.

Table 4-1: Procedure and Data Collection on Patients with an Attempted Implant

Study Procedures/Data Collection	Enroll-ment	Nanostim LP Implant	Pre-Discharge (0 / +2 days)	2- week post implant (± 7 days)	6- Months post implant (± 60 days)	Every 6 Months through 7 years (± 60 days)
Informed Consent, Inclusion/ Exclusion and Demographics	X					
Implant Procedure		X				
Device Interrogation/Electrical Measurements*		X	X	X	X	X
ADEs, SADEs, and Complications		X	X	X	X	X

*Device interrogation: capture threshold, R-wave amplitude, and pacing impedance

Table 4-2: Procedures and Data Collection for Rollover Patients

Data Collection	Enrollment	Every 6 Months through 7 years post-implant (± 60 days)
Informed Consent	X	
Device Interrogation/ Electrical Measurements*	X	X
ADEs, SADEs, and Complications**	X	X

* Device interrogation: capture threshold, R-wave amplitude, and pacing impedance
**For Rollover patients, collection of ADEs, SADEs, and complications will begin after the final visit of the Leadless IDE study and after patient signs consent to participate in the PAS study.

4.4 Study Oversight

The study will include a clinical events committee (CEC). The CEC is responsible for providing an independent review and adjudication of reportable events, such as adverse device effects, serious adverse device effects, complications and deaths as required by the study protocol. Membership cannot include Investigators participating in the study.

4.5 Study Endpoints

The study will characterize the complication rate of the Nanostim LP system. Each complication will be reported and summarized separately.

The following related Nanostim LP system complications will be reported:

- Cardiac perforation
- Dislodgement
- Elevated pacing thresholds or loss of capture
- Vascular Access Site Complications
- Other complications that are considered related to the Nanostim LP system

The following data will be summarized on patients whose implanted devices are either deactivated or retrieved for any reason (end of life, device upgrade, elective explant, other) during the course of the study:

- Remaining longevity of current LP (if not at end of life)
- Number and proportion of patients in the following categories:
  - LP explanted and another LP implanted
  - LP explanted and a pacing or defibrillation lead implanted
  - LP disabled and another LP implanted adjacent to existing LP
  - LP disabled and a pacing or defibrillation lead implanted adjacent to existing LP
  - Other

The above data on disabled and retrieved devices will be pooled across the post-approval study and the EU Leadless Observational Study. The combined data from the PAS and the Leadless Observational Study is expected to total up to approximately 250 patients with disabled or retrieved devices.

The following additional data will be collected during the study:

- Demographic information - Gender, age, ethnicity, race, cardiac disease history, arrhythmia history, indication for pacemaker implant, and cardiac medications
- Implant success rate and reasons for unsuccessful implant
- Anticoagulants/Antiplatelet/Antithrombotic therapy prior and during implantation
- Number of device repositionings required during implantation
- Final anatomic location of LP placement
- Mortality
- Number of attempted device retrievals of leadless pacemaker post implantation

- Percentage of successful device retrievals of leadless pacemaker post implantation (successful device retrieval is defined as retrieval of the device without any complications following 30 days of the retrieval procedure)

4.6 Sample Size

For adverse events occurring at a rate of 1%, the sample size required for the adverse event rate to have a 90% CI half width of at most 0.5%, the sample size required is 1700 patients. Assuming a 5% unsuccessful implant rate, and an annual attrition rate of 14.8%, the expected number of patients at 7 years is 526 (=1700 x 0.95 x (1-0.148) ^7). Serious adverse device effects have not occurred in the Leadless II IDE study cohorts (primary as well as total cohort) beyond 30 days. Therefore, in the long term, device related serious adverse events are expected to occur at a very low rate. Assuming a late adverse event rate of 0.3%, with 526 patients with follow-up complete through 7 years, the 90% CI width is within 1%.

4.7 Patient Retention

One or more of the following strategies are either employed or will be considered to retain patients in the study through the follow-up period:

- Screening potential participants for willingness to participate over the long-term
- Fully informing participants of commitment and requirements of study
- Providing patient scheduling tools for sites
- Collecting names of personal contacts and proxies
- Encouraging site personnel to maintain regular contacts with participant
- Utilizing wide window (± 60 days) to allow scheduling flexibility, particularly for the longer term follow-up visits
- Providing travel expense reimbursement to patients
- Providing reminder tools to patients
- Assisting sites in transferring a patient to another study site when a patient moves
- Requiring sites to report adverse events upon notification rather than waiting until the patient’s next follow-up visit
- Providing SJM technical expertise during explant and implant procedures in order to retrieve the explanted device for analysis

5. Training Program

St. Jude Medical has developed a phased, standardized methodology for providing physicians with education and training on the safe implantation and retrieval of a Nanostim LP, and care for their Nanostim patients. The goal of the training program is to insure that physicians are proficient with the implanting technique and maximize positive clinical outcomes for the patients.

> The phased training program is intended to ensure that implanting physicians are adequately trained and informed regarding the potential occurrence of adverse events and appropriate device and patient selection.

The training program will be mandatory, requiring completion of multiple modules prior to a physician receiving certification. The training is similar to that provided to the physicians who participated in the Leadless II study, and has been revised to include key learnings from the worldwide Nanostim clinical experience. There are multiple phases to the training, encompassing 7 modules, as shown below:

- Nanostim Didactic Training (Module 1)
- Hands-On Training
  - Implant Demonstration with Catheter (Module 2)
  - Animal Lab Training (Module 3) **or** Virtual Reality Training (Module 5)
  - Video Compendium (Module 4)
- Case Observation (live or recorded; Module 6a)
- Ten Cases Supported by SJM Certified Personnel (Module 6b)
- Site-Training and onboarding (Module 7)

To participate in the training program, physicians must be qualified to implant pacemakers and have an established practice affiliation with an institution that has resources to supported leadless pacemaker implantation. High resolution fluoroscopy equipment and proper emergency facilities for cardioversion, defibrillation, pericardiocentesis and cardio-pulmonary resuscitation re required for all Nanostim cases.

5.1 Module 1: Nanostim Didactic Training

The training program begins with a didactic session. This session provides a thorough overview of the Nanostim Leadless Pacemaker System including: system components, handle operations, procedural overview, and specific tips for optimizing outcomes. The training will also include an overview of the clinical study design and outcomes.

5.2 Module 2: Hands-on Implant Demonstration

The hands-on implant demonstration with catheter provides training and instruction on the proper set-up of the delivery and retrieval catheters, as well as the delivery and retrieval catheter handle operations. Demonstration and reinforcement of the procedure steps will include particular emphasis on critical steps and techniques to avoid complications. After watching the demonstration, the physician must be able to demonstrate handle functions, review steps of the procedure and identify key parts of the procedure to avoid complications such as perforations and dislodgements.

5.3 Module 3: Animal Lab Training

The Nanostim animal lab training encompasses multiple components to reinforce elements specified in the Instructions for Use:

- Device packaging and preparation review (18F introducer, delivery and retrieval catheters)
- Merlin and Link set-up and troubleshooting

The physician will perform at least 3 deliveries, repositionings, and retrievals of the Nanostim LP with emphasis on best and worst practices. During this training, the physician and trainer will also discuss patient selection for initial cases. There will be an emphasis on performing the initial patient implants as close as possible to the animal training lab.

5.4 Module 4: Video Compendium

The video compendium was designed in order to have a resource for physicians on key procedure steps, as well as clear visualization of what not to do. The compendium is to be watched during the initial training process, and remains available as a resource to be consulted as needed. The video compendium specifically demonstrates:

- 18F Sheath introduction
- Orienting the deflection plane
- LP introduction into the IVC
- Protecting the helix
- System advancement into the right atrium
- Proper introduction into the right ventricle

- Opacification of the right ventricle
- Multi-plane confirmation of desired LP position
- Retracting the protective sleeve
- Engaging the endocardium
- Mapping endocardium before implant
- Implant sequence
- Deflection Test
- Programming-acceptable electrical measurements
- LP release and catheter removal
- Venous access closure and hemostasis

5.5 Module 5: Virtual Reality Simulator

The virtual reality simulator is a new tool available to physicians as part of the training program. It allows the user to replicate implantation and retrieval of a Nanostim LP. The simulator is part of the initial training program, and can also be used as part of a refresher course for users who have not performed a case for a prolonged period of time or require additional training. Simulator training is designed to emphasize proper and improper technique and includes real-time error messages to notify the operator of catheter handling that is not in line with the device labeling. This tool teaches the physician how to avoid excessive force or pushing, excessive torqueing or torqueing too fast. The simulator is also used to demonstrate proper and improper techniques for the following:

- Protecting the helix
- Utilizing appropriate speed of catheter movement within the vasculature
- Introduction of the LP
- Covering of the helix
- Advancing the catheter up the inferior vena cava
- Entering the right ventricle
- Opacifying the right ventricle
- Right anterior oblique and left anterior oblique views
- Achieving septal orientation

- Retracting the protective sleeve
- Helix engagement of the endocardium
- Mapping the endocardium
- Implant sequence
- Tether mode
- Deflection test
- Electrical assessment
- Re-dock and reposition
- LP Release
- Catheter removal

5.6 Module 6: Physician Case Observation and Supported Cases

After completion of the above training program components, and prior to performing any live cases, all physicians are required to observe either a live or recorded Nanostim leadless pacemaker implant. Following this, all new Nanostim implanters must have technical and implant support and in-case training provided by SJM certified personnel for their initial 10 cases. After each case, the SJM certified personnel will review the case or elements from previous cases, with particular emphasis on key parts of the case and desired implant techniques.

5.7 Module 7: Site Training and Onboarding

Prior to the first Nanostim LP case, supporting electrophysiology lab staff are required to attend a Nanostim in-service to better understand system preparation and set-up, packaging, handle operations, programming, and review of patient selection criteria. All hospital personnel who will support Nanostim implants should attend a Nanostim training session.

5.8 Physician Certification

Upon successful completion of all required training steps, including the 10 supported cases, the physician will receive a certification from St. Jude Medical to perform percutaneous leadless pacemaker implants or retrievals independently using the Nanostim LP System.

6. Benefit-Risk Assessment

The data supporting the probable benefits of the Nanostim Leadless Pacemaker are primarily based on the Leadless II IDE clinical study. The EU implant experience provides additional information supporting the benefits of the Nanostim Leadless Pacemaker. Use of the Nanostim Leadless Pacemaker in clinical studies confirms the soundness and the benefits of the leadless pacing approach for patients indicated for a single-chamber ventricular pacemaker. No unanticipated serious adverse device effects occurred in any patient during the study, and the device performed as intended. The Leadless II study met the pre-specified performance goals for both primary effectiveness (pacing and sensing) and primary safety (freedom from serious adverse device effects) at six months follow up. The studies also demonstrated that the device can be retrieved chronically and that the mean device longevity with actual use conditions is expected to approximate 15 years.

6.1 Retrievability

The Nanostim Leadless Pacemaker is designed to be either acutely or chronically retrieved. There are several potential situations in which it would be desirable to retrieve a Nanostim Leadless Pacemaker including but not limited to: battery reaches recommended replacement time (RRT), endovascular infection or patient requiring an upgrade to a different device type (implantable defibrillator, dual chamber pacemaker, CRT device).

Early human experience supports the safety and effectiveness of retrieval in the chronic setting. In the Leadless II IDE study, 7 patients with a chronically implanted leadless pacemaker underwent successful device retrieval at a mean of 160+/- 180 days (median = 100 days; range 1-413 days). The reasons for retrieval were pacing threshold elevation (n = 4), worsening heart failure requiring CRT (n = 2) and elective explant (n = 1). Three patients received a new Nanostim leadless pacemaker implant, two patients received conventional pacemakers and the two patients with worsening heart failure were upgraded to conventional biventricular pacemakers. Furthermore, at the device end of life there are presently 4 options available to offer continued bradycardia pacing: (1) disable the existing leadless pacemaker and place a new leadless pacemaker, (2) disable the existing leadless pacemaker and implant a transvenous pacemaker, (3) retrieve the leadless pacemaker and place a new leadless pacemaker and (4) retrieve the leadless pacemaker and implant a conventional pacemaker.

The ability to chronically retrieve the device reduces the long-term risks to the patient because there is no hardware residing in veins or subcutaneous pockets. Compared to transvenous systems, there is no lead or other hardware remaining in the vasculature creating a risk for infection or taking up needed intravascular space.

6.2 Longevity

The Leadless II clinical study shows that the Nanostim Leadless Pacemaker longevity is expected to be approximately 15 years, and potentially as high as 21 years depending on specific patient pacing needs. This is comparable to and perhaps greater than single chamber transvenous pacemakers.

6.3 Acute and Chronic Complications - Leadless vs Transvenous

The clinical risks most frequently encountered with existing pacemaker systems are related to the pacemaker pocket and lead, therefore they are not relevant to the Nanostim Leadless Pacemaker System. **Table 6-1** summarizes the benefits of a leadless pacing system when compared to transvenous pacemaker systems.

Table 6-1: Summary of Risks and Benefits of a Leadless Pacing System

Description	Risk or Benefit	Relation to standard pacemaker systems
No pocket infection	Benefit	Unique to leadless pacemakers
No pulse generator pocket hematoma or seroma	Benefit	Unique to leadless pacemakers
No lead-induced tricuspid regurgitation	Possible benefit	Unique to leadless pacemakers
No lead fractures or connector problems (no intra-system connections)	Benefit	Unique to leadless pacemakers
No risk of venous obstruction	Possible benefit	Unique to leadless pacemakers
No pectoral pocket: greater patient comfort postoperatively and elimination of scars and generator bulge	Benefit	Unique to leadless pacemakers
No venous access related pneumothorax	Benefit	Unique to leadless pacemakers
Dislodgement	Risk	Also a risk with standard pacemaker system, although the sequelae and clinical significance may be different
Perforation	Risk	Also a risk with standard pacemaker system, although the sequelae and clinical significance may be different
Groin access complications	Risk	Unique to leadless pacemakers

6.3.1 Complications with Transvenous Pacemaker Systems

Although still a good option for many patients, transvenous pacemakers have been shown to have complications. The literature provides 3-month complication rate range of 5.5% and 11.2%.

- Pakarinen et al. reported a 3-month complication rate of 11.2% in patients receiving a conventional single-chamber pacemaker (n = 143) in a 567-patient study.[27]
- In the prospective FOLLOWPACE study involving 1517 pacemaker patients at 23 centers, 12.4% patients developed pacemaker complications through 2 months of implant.[14] After excluding from the analysis any reported atrial lead complications (1 perforation and 27 dislodgements), the pacemaker complication rate was still high at 10.5% (160 out of 1517 enrolled patients) at 2 months.
- The pacing system-related complication rate at four months evaluated in 447 patients enrolled in the EnRhythm MRI study was 8.3%.[29]
- The Mode Selection in Sinus Node Dysfunction Trial enrolled 2010 patients and the complication rates reported were 4.8% at 30 days, 5.5% at 90 days, and 7.5% at 3 years.[30]

6.3.2 Nanostim Leadless Pacemaker

In the Leadless II study the SADE rate for 300 patients in the primary cohort after six months follow up of 6.7%. This included device dislodgement in 1.7%, cardiac perforation in 1.3%, elevated pacing thresholds requiring device retrieval and re-implantation in 1.3%, and vascular complications in 1.3% of patients. The SADE rate through six months for the full cohort of 526 patients was 6.5%. This included cardiac perforation in 1.5%, device dislodgement in 1.1%, and device retrieval due to elevated pacing thresholds in 0.8% of patients. There were no device related deaths. As evidenced in the Kaplan-Meier curves (**Figure 3-7** and **Figure 3-8**) based on data from the primary cohort of 300 patients and the full cohort of 526 patients, there have been no reports of SADEs beyond 30 days from implant.

6.3.3 Perforation

Similar to transvenous systems, perforation is one of the risks associated with the use of the Nanostim LP. The rate of perforation for transvenous pacemaker leads varies between 0.4% to 1.2%.[4,14,31] In another study, the incidence of pericardial tamponade or large pericardial effusion was 1.7%.[32] Given that the Nanostim LP is a new technology with a new implant procedure for all but one of the 100 implanters in the study, the observed myocardial perforation rate is considered to be acceptable when compared to that of a mature therapy and may even decrease over time as physicians gain more experience with this technology.

6.3.4 Dislodgement

Similarly, the risk of dislodgement is a risk associated with use of either a conventional transvenous system or the Nanostim LP. In the Leadless II study total cohort of 526 patients the rate of dislodgement was 1.1%. This observed rate falls within the range seen in the published literature for transvenous pacing leads (up to 2.3%).[14] Of note, all dislodged Nanostim LPs were successfully retrieved without further complications in the clinical study.

6.3.5 Femoral Vein Access

The risk related to femoral vein access is unique to the Nanostim LP since it is not generally applicable to transvenous systems. The risk of venous access site complications was 1.3% in the Leadless II study. This compares to the rate for severe venous thrombosis with transvenous systems, which is one of the causes for venous obstruction, reported to be 1 to 3%.[33-36]

The rate of venous access site complications is also consistent with the experience using large caliber sheaths for percutaneous mitral valve repair and transcatheter valve delivery. The most detailed information on venous access site bleeding associated with percutaneous mitral valve repair comes from the EVEREST II High Risk Registry, in which there were 9 bleeding events in a cohort of 78 patients (11.5%).[37] In a meta-analysis of 16 studies, the rate of vascular complications requiring intervention was 1% (20/2002) and the rate of major bleeding requiring transfusion was 9.7% (253/2599), although the bleeding sites were not specified.[38] Vascular-access related complications associated with percutaneous pulmonary valve delivery range from 0% - 6.9% in smaller trials, and are commonly about 1% in larger trials of over 100 patients.[39-43] Thus, the 1.3% rate of venous complications with the Nanostim LP is favorable compared to other large sheath, femoral access procedures which have reported rates in the range of 1% to 11.5%.

6.4 Conclusions

In summary, given the benefits of the Nanostim LP and the similar complication rates associated with alternative therapies, the benefits of the device outweigh the risks. The observed safety and effectiveness of the Leadless Pacemaker supports its use as an alternative to transvenous pacemakers in patients indicated for single-chamber ventricular pacing. A robust training program will support safe use of the Nanostim LP upon commercialization and event rates will continue to be monitored in post-approval studies to ensure this balance remains favorable.

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Appendix A Response to Agency Questions

St. Jude Medical has prepared the following to provide the Advisory Committee with information and perspective on the Agency's discussion questions. The Agency questions are shown in bold and italic font, with the SJM perspective in standard font.

FDA QUESTION #1

A. Please discuss the clinical significance and any concerns you might have for the rate of occurrence of each of the following adverse events observed to occur at implant with leadless pacemaker devices as compared to traditional pacemakers.

- ***Perforation***
- ***Pericardial Effusion***
- ***Dislodgement***
- ***Embolization***
- ***Other events. (e.g. stroke, arrhythmia)***

<u>SJM Perspective</u>

The events listed above occurred at rates that were in the range or slightly above those reported for conventional pacemakers with leads and were treated successfully using techniques similar to those used to treat these events when they occur with a conventional pacemaker. In addition, a number of significant complications (lead-related as well as pocket-related) did not occur; these are eliminated due to the design of the Nanostim LP. Overall, the short-term safety profile of the Nanostim LP is comparable to that of conventional pacemakers, as shown in **Table 3-6**. The large majority of events reported in the Leadless II study were noted in the first two weeks post-implantation and none occurred after the 30-day early post-procedure period. Long-term data on the Nanostim LP will continue to be gathered, as described in Section 4 on the Post-Approval Study.

B. Please identify any subgroups of patients (e.g., based on anatomical characteristics, demographics, etc.) as having an increased risk based on the adverse event rates associated with these devices.

SJM Perspective

In the Leadless II study there were no subgroups of patients identified as having an increased risk for serious adverse device effects (SADEs), at the 5% significance level. This is based on an analysis conducted to assess which, if any, variables were predictors of adverse events in the Leadless II study. Univariate logistic regression modelling used the following explanatory variables: age, BMI, sex, prior cardiac intervention [coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), stent, atherectomy, or ablation], use of anticoagulants, use of antiplatelets, and whether or not repositioning had been attempted. Results of this analysis are detailed in **Table 3-9** and demonstrate that, at the 5% significance level, there were no significant predictors of having an SADE. A stepwise multivariate model led to the same result; there were no significant predictors of having an SADE.

C. Please discuss what measures you would recommend to ensure that implanting physicians are adequately trained/informed regarding the potential occurrence of adverse events and appropriate device and patient selection.

SJM Perspective

The phased training program proposed by SJM is intended to ensure that implanting physicians are adequately trained and informed regarding appropriate device and patient selection, the potential occurrence of adverse events and how to minimize the likelihood that they occur. The training program is discussed in detail in Section 5, and summarized here.

The SJM Nanostim LP training program will be mandatory, requiring the completion of multiple modules prior to receiving certification. The training program is similar to that provided to physicians who participated in the Leadless II study, and has been revised to include key learnings from the worldwide clinical experience with implanting the Nanostim LP.

There are multiple phases to the training program, encompassing 7 modules, as shown below:

- Didactic Training (Module 1)
- Hands-On Training
    - Implant Demonstration with Catheter (Module 2)
    - Animal Lab Training (Module 3) **or** Virtual Reality Training (Module 5)
    - Video Compendium (Module 4)
- Case Observation (live or recorded; Module 6a)

- Ten Procedures with Technical and Implant Support and In-Case Training by SJM Certified Personnel (Module 6b)
- Site-Training and onboarding (Module 7)

To participate in the training program, physicians must be qualified to implant pacemakers and have an established practice affiliation with an institution that has resources to supported leadless pacemaker implantation. SJM looks forward to the Committee's discussion on this topic and any suggestions on improving upon what has been proposed.

FDA QUESTION #2

A. Please comment on how to best collect data for acute performance/ implant experience in the post- approval setting.

i. Acute performance can be defined as 30 days from implant. The adverse events most likely to occur within these 30 days are dislodgements, threshold increases, etc. Implant experience can be defined as pre-discharge/24 hours from implant. The events most likely to occur within these 24 hours include groin complications, hematoma, vascular issues, and perforations. Please indicate which issues you believe should be addressed through collection of post approval data.

SJM Perspective

SJM has proposed a 7-year patient post-approval study that will collect all reported adverse events, including those reported through pre-discharge/24 hours from implant, through 30 days from implant, and over the duration of the study. Implant adverse events such as cardiac perforation, vascular access site complications (including hematoma and groin complications), and other complications considered to be related to the Nanostim LP will be collected. Additionally, adverse events expected to occur in the acute phase through 30 days, such as dislodgements and elevated pacing thresholds or loss of capture, will be collected. The PAS follow-up schedule in the first 30 days post implant is similar to that in the IDE study and clinical study sites are also asked to report adverse events as they occur and not wait until the next follow-up visit. Additional details are provided in Section 4.5.

ii. FDA would expect sample sizes large enough to provide estimates of adverse events to a specific resolution with confidence intervals (keep in mind the high occurrence of acute adverse events).

Please indicate which sample size is appropriate based on the table below.

ODE assumed complication rate	***Target CI Width***	***Minimum Sample Size Needed***	***Upper limit of the 95% CI***
1%	***+/- 0.5%***	***1741***	***1.6%***
1%	***+/- 1.0%***	***497***	***2.3%***
1%	***+/- 1.5%***	***251***	***3.2%***

SJM Perspective

The SJM post-approval study proposal includes a sample size of 1700, which is large enough to provide estimates of adverse events occurring at a rate of 1% to within a 90% confidence interval width of 1%. The proposed sample size is detailed in Section 4.6.

B. FDA acknowledges that the long-term performance of leadless pacemakers is not well understood at this time. The estimated battery life for these devices is predicted to be anywhere from 6 to 12 years.

i. Please comment on the types of late life failures you would expect to be important to capture, given the design of leadless pacemakers.

SJM Perspective

As described above, any adverse events reported during the 7-year post-approval study, including device failure, and the type of late failures, will be collected. Because long-term data on leadless pacemakers are not yet available, SJM believes this comprehensive approach is appropriate.

ii. Based on the current paradigm for post-approval studies for leads, a complication-free rate is used as the endpoint for long-term performance. Please comment on the appropriateness of this endpoint for leadless pacemakers or suggest an alternative endpoint for long term performance of these devices.

SJM Perspective

SJM has noted that in the Leadless II IDE study, SADEs occurred early in the post-procedure follow-up period. The PAS will therefore collect and report on implant adverse events occurring through discharge/24 hours, and adverse events occurring through 30 days. SJM also understands the importance of continuing to collect and report on SADEs in long-term follow-up within the PAS. Therefore, SJM believes that an endpoint of freedom from complications is clinically appropriate for long-term performance.

iii. Please provide recommendations for ways to insure the completion of a long-term post approval study considering the following:

a. the difficulty in implementing such a study;

b. patients lost to follow-up over the course of a long study;

c. the ability to characterize end of life device failures; and

d. the ability to accurately collect device disposition when a new device is placed.

SJM Perspective

SJM has significant experience with conducting clinical studies of similar size and duration, and has developed a range of patient retention strategies, that include:

- Screening potential participants for willingness to participate over the long-term
- Fully informing participants of commitment and requirements of study
- Providing patient scheduling tools for sites
- Collecting names of personal contacts and proxies
- Encouraging site personnel to maintain regular contacts with participant
- Utilizing wide window (± 60 days) to allow scheduling flexibility, particularly for the longer term follow-up visits
- Providing travel expense reimbursement to patients
- Providing reminder tools to patients
- Assisting sites in transferring a patient to another study site when a patient moves
- Requiring sites to report adverse events upon notification rather than waiting until the patient’s next follow-up visit
- Providing SJM technical expertise during explant and implant procedures in order to retrieve the explanted device for analysis

iv. Please comment on the ideal duration of follow-up time to assess long term performance of leadless pacemakers.

SJM Perspective

Based on feedback from the Agency, SJM is proposing to conduct a 7-year post-approval study. SJM believes this study duration will lead to important data real-world collection that can be used to assess the long term performance of the Nanostim LP. Additionally, SJM believes that there will be an adequate number of patients (over 100 patients) at this time to characterize patient management at device end of life.

C. FDA is interested in collecting data on what clinicians decide to do with devices after they reach end of life (EOL).

FDA foresees four (4) likely scenarios for device EOL:

- ***Explant Leadless Pacemaker and implant***
    - ***another LP***
    - ***a traditional pacemaker system***
- ***Turning OFF the existing LP and implanting an adjacent LP next to it***
- ***Turning OFF the existing LP and implanting an adjacent transvenous pacemaker next to it.***

FDA expects that physicians may prefer one or two approaches over the others. It should be noted that the LP is expected to be fully encapsulated, which differs from traditional pacemaker/lead systems. FDA expects this aspect of the PAS to be observational.

SJM Perspective

SJM agrees that longer-term data are required to better determine to what degree the LP may become encapsulated and retrieved. Available data to date indicate that devices do not become encapsulated or are only partially encapsulated many months or even years after implant. In the pre-clinical experience in the ovine model, as well as in the early human experience, device retrieval has been successful in all attempts. In contrast to transvenous leads which adhere to the vascular system and to cardiac structures, the LP is only attached to the myocardium at the helix. Furthermore, as compared to leads, the retrieval catheter allows for the transmission of forces directly to the body of the LP and thus the helix. SJM agrees to characterize how patients are managed at device end of life by summarizing the number and proportion of patients in each of the following categories, as described in Section 4.3:

1. LP is explanted and another LP is implanted
2. LP is explanted and a pacing or defibrillation lead is implanted
3. LP is disabled and another LP is implanted adjacent to the existing LP
4. LP is disabled and a pacing or defibrillation lead is implanted adjacent to the existing LP
5. Other

Please comment on the following questions:

i. Given the observational nature of the Post Approval Study, what criteria should be used to determine the sample size i.e. acceptable rates of occurrence and precision of rates?

SJM Perspective

As described in Section 4.6, the proposed sample size of 1700 is large enough to provide estimates of adverse events occurring at a rate of 1% to within a 90% confidence interval width of 1%. This sample size is expected to result in approximately 526 patients with complete 7-year data and assumes a 5% unsuccessful implant rate and an annual attrition rate of 14.8%; these assumptions are likely conservative. Assuming a late adverse event rate of 0.3%, a sample size of 526 patients will result in a 90% confidence interval width of within 1%.

ii. Regarding the scenarios outlined above, what is an appropriate follow-up time to observe for new device interactions with the previously implanted device?

SJM Perspective

SJM proposes to follow patients whose device reaches end of life for a minimum of 30 days after the intervention to replace the device. Patients who receive another LP (scenario 1 or scenario 3 described above) will continue to be followed until 7 years from the time of original implant when the study follow-up period ends.

iii. Please recommend an approach to evaluate device removal/extraction i.e. how often it is attempted, success rates, and complications associated with removal/extraction?

<u>SJM Perspective</u>

In the Nanostim LP post-approval study, data will be gathered on the approaches utilized for device removal and retrieval, as well as device deactivation. SJM will report on complications associated with the retrieval procedure through 30 days. SJM will also report on the explant success rate and the success rate for implanting a replacement device (LP or transvenous leads).

FDA QUESTION #3

In the absence of data on long term performance and end-of-life options for leadless pacemakers, please comment on content and points to address for appropriate labeling regarding extractions, replacements, and best practices at this time.

<u>SJM Perspective</u>

Because it has been demonstrated in the Leadless II study that the Nanostim LP can be successfully retrieved, SJM has proposed a robust training program and device labeling that provide detailed instruction on device retrieval and replacement options. As is the case with transvenous leads, there may be circumstances in which the risk-benefit assessment favors not extracting the device. The training program will include detailed information as to the potential risks associated with retrieval so that clinicians can make the appropriate individualized decision for a specific patient.

Appendix B Number of Patients at Each Leadless II Investigational Site

Site Number	Investigational Site	Site Location	Principal Investigator	Patients Enrolled
US Sites				
1	Sparrow Research	Lansing, MI	John Ip, MD	33
2	Mount Sinai Hospital	New York, NY	Srinivas Dukkipati, MD	23
3	Aurora Medical Group	Milwaukee, WI	Imran Niazi, MD	20
4	Naples Community Hospital	Naples, FL	Kenneth Plunkitt, MD	19
5	Premier Cardiology, Inc	Newport Beach, CA	Rajesh Banker, MD	18
6	Central Baptist Hospital	Lexington, KY	Gery Tomassoni, MD	17
7	New York Presbyterian Hospital/Cornell University	New York, NY	James Ip, MD	17
8	Huntington Memorial Hospital	Pasadena, CA	Mayer Rashtian, MD	16
9	Methodist University Hospital	Memphis, TN	James Porterfield, MD	14
10	South Denver Cardiology Associates PC	Littleton, CO	Sri Sundaram, MD	14
11	Athens Regional Medical Center	Athens, GA	Kent Nilsson, MD	14
12	LeBauer HeartCare	Greensboro, NC	James Allred, MD	13
13	University Hospitals of Cleveland	Cleveland, OH	Judith Mackall, MD	12
14	The Cleveland Clinic Foundation	Cleveland, OH	Daniel Cantillon, MD	12
15	Intermountain Heart Rhythm Specialists	Murray, UT	T. Jared Bunch, MD	12
16	Mercy Hospital St. Louis	St. Louis, MO	Amit Doshi, MD	12
17	St. John Hospital and Medical Center	Detroit, MI	Sohail Hassan, MD	11
18	Kansas University Medical Center	Kansas City, KS	Dhanunjaya Lakkireddy, MD	11
19	USC University Hospital	Los Angeles, CA	Rahul Doshi, MD	11

Site Number	Investigational Site	Site Location	Principal Investigator	Patients Enrolled
20	Trinity Health-Michigan d/b/a Michigan Heart	Ann Arbor, MI	Jihn Han, MD	11
21	Sequoia Hospital	Redwood City, CA	Rob Patrawala, MD	11
22	University Hospital - Univ. of Alabama at Birmingham	Birmingham, AL	Harish Doppalapudi, MD	10
23	Munson Medical Center	Traverse City, MI	Brian Jaffe, MD	10
24	Scripps Health	La Jolla, CA	Steven Higgins, MD	9
25	Mayo Clinic	Rochester, MN	Paul Friedman, MD	8
26	Cardiac Arrhythmia and Pacemaker Center	Roslyn, NY	Joseph Levine, MD	8
27	Heart Center Research, LLC.	Huntsville, AL	Jay Dinerman, MD	7
28	Fairview Southdale Hospital	Edina, MN	Quan Pham, MD	7
29	ClinicalTex Research, LLC	Amarillo, TX	Sammy (Lane) Cox, MD	7
30	Jersey Shore University Medical Center	Neptune, NJ	Ashish Patel, MD	6
31	Florida Hospital Orlando	Orlando, FL	Scott Pollak, MD	6
32	Redmond Regional Medical Center	Rome, GA	Robert Styperek, MD	6
33	St. Elizabeth Medical Center – South Unit	Edgewood, KY	Mohamad Sinno, MD	6
34	Regional Cardiology Associates	Sacramento, CA	Gearoid O'Neill, MD	6
35	Advocate Christ Medical Center	Oak Lawn, IL	Manoj Duggal, MD	5
36	Duke University Medical Center	Durham, NC	Brett Atwater, MD	5
37	Ochsner Medical Center	New Orleans, LA	Michael Bernard, MD	5
38	Fogarty Institute	Mountain View, CA	Bing Liem, MD	5
39	University of Pittsburgh Medical Center	Pittsburgh, PA	Sandeep Jain, MD	4
40	Lahey Clinic Medical Center	Burlington, MA	Bruce Hook, MD	4
41	Massachusetts General Hospital	Boston, MA	Moussa Mansour, MD	4

Site Number	Investigational Site	Site Location	Principal Investigator	Patients Enrolled
42	South Texas Cardiovascular Consultants	San Antonio, TX	Charles Machell, MD	4
43	Parkview Research Center	Fort Wayne, IN	Michael Mirro, MD	4
44	Integris Baptist Medical Center	Oklahoma City, OK	Richard Lane, MD	3
45	WellSpan Health	York, PA	Lyle Siddoway, MD	3
46	University of Chicago	Chicago, IL	Martin Burke, MD	2
47	Memorial Hermann Hospital	Houston, TX	Ramesh Hariharan, MD	2
48	Inova Fairfax Hospital	Fairfax, VA	Adam Strickberger, MD	1
49	Tufts Medical Center	Boston, MA	Jonathan Weinstock, MD	1
50	Orlando Health	Orlando, FL	David Bello, MD	1
US Total				**470**
Sites located outside the U.S.				
1	Foothills Medical Centre	Calgary Alberta, Canada	Derek Exner, MD	20
2	Vancouver General Hospital (U of BC)	Vancouver British Columbia, Canada	Matthew Bennett, MD	16
3	Royal Adelaide Hospital	Adelaide South Australia	Prashanthan Sanders, MD	7
4	Princess Alexandra Hospital	Wooloongabba Queensland, Australia	John Hill, MD	5
5	Institut de Cardiologie de Montreal (Montreal Heart Inst.)	Montreal Quebec, Canada	Bernard Thibault, MD	4
6	Southlake Regional Health Centre	Newmarket Ontario, Canada	Bernice Tsang, MD	4
Sites outside the U.S. Total				**56**
Worldwide Total:				**526**