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The LEADLESS II Study
A safety and effectiveness trial for a leadless pacemaker system
Study Document No: SJM-CIP-10226
Version L
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Sponsor

St. Jude Medical (now Abbott)
Cardiac Rhythm Management
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U.S.

Clinical Investigation Plan

INVESTIGATION PLAN

The LEADLESS II Study

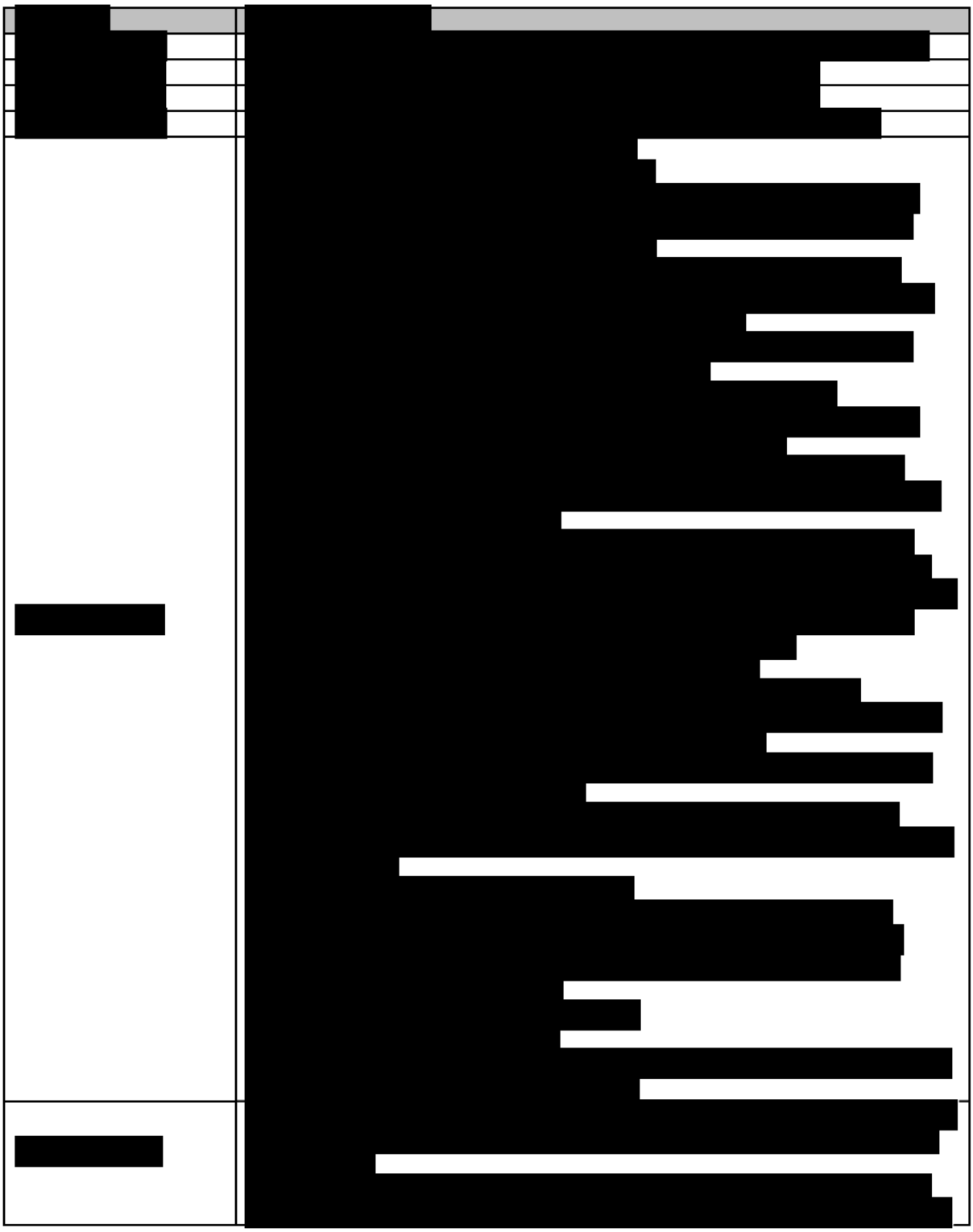
A safety and effectiveness trial for a leadless pacemaker system

Study Document No: SJM-CIP-10226/Rev L
July 13, 2018

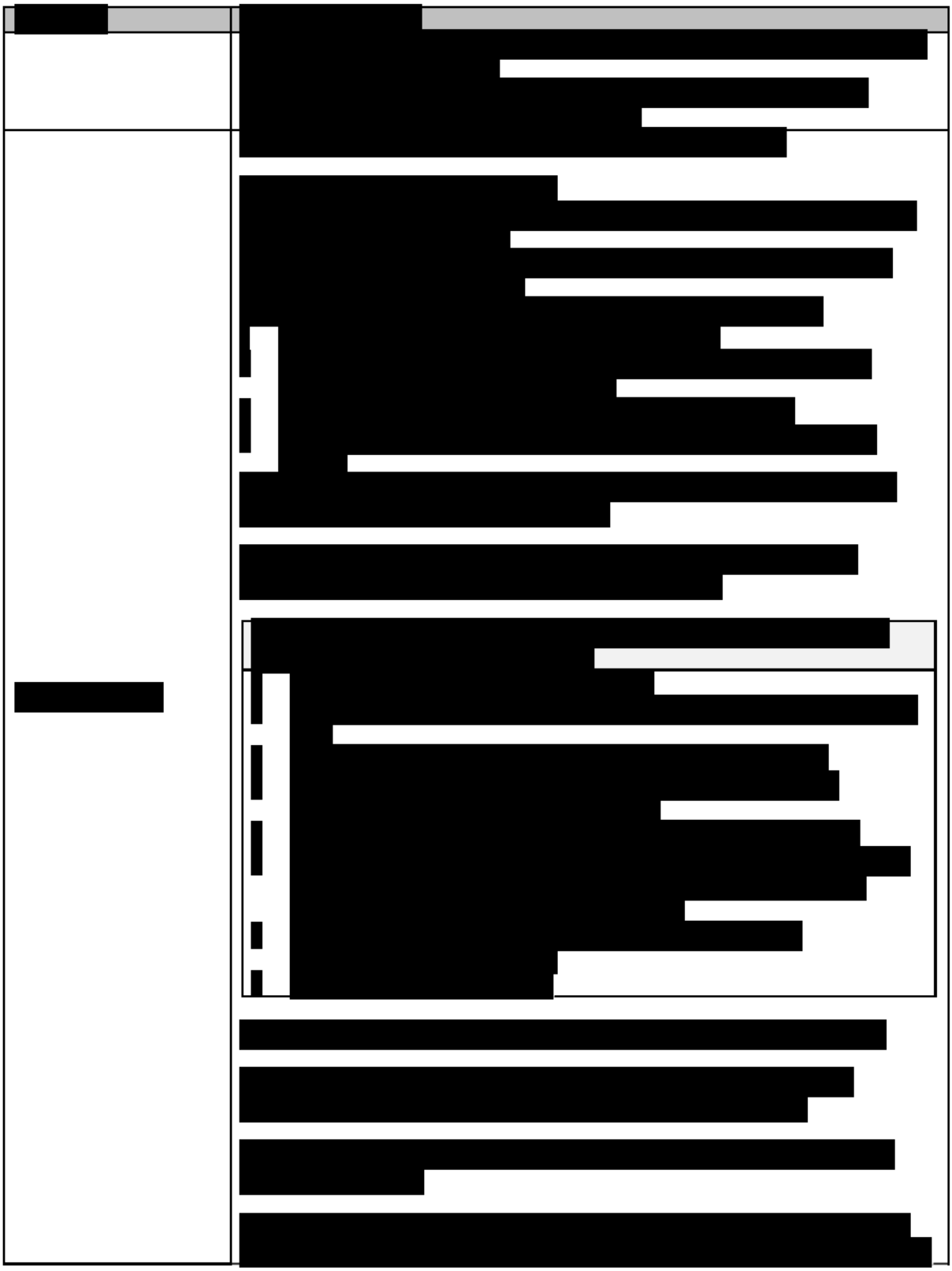
IDE Number: [redacted]

Clinical Investigation Plan

1.0 Revision Change History

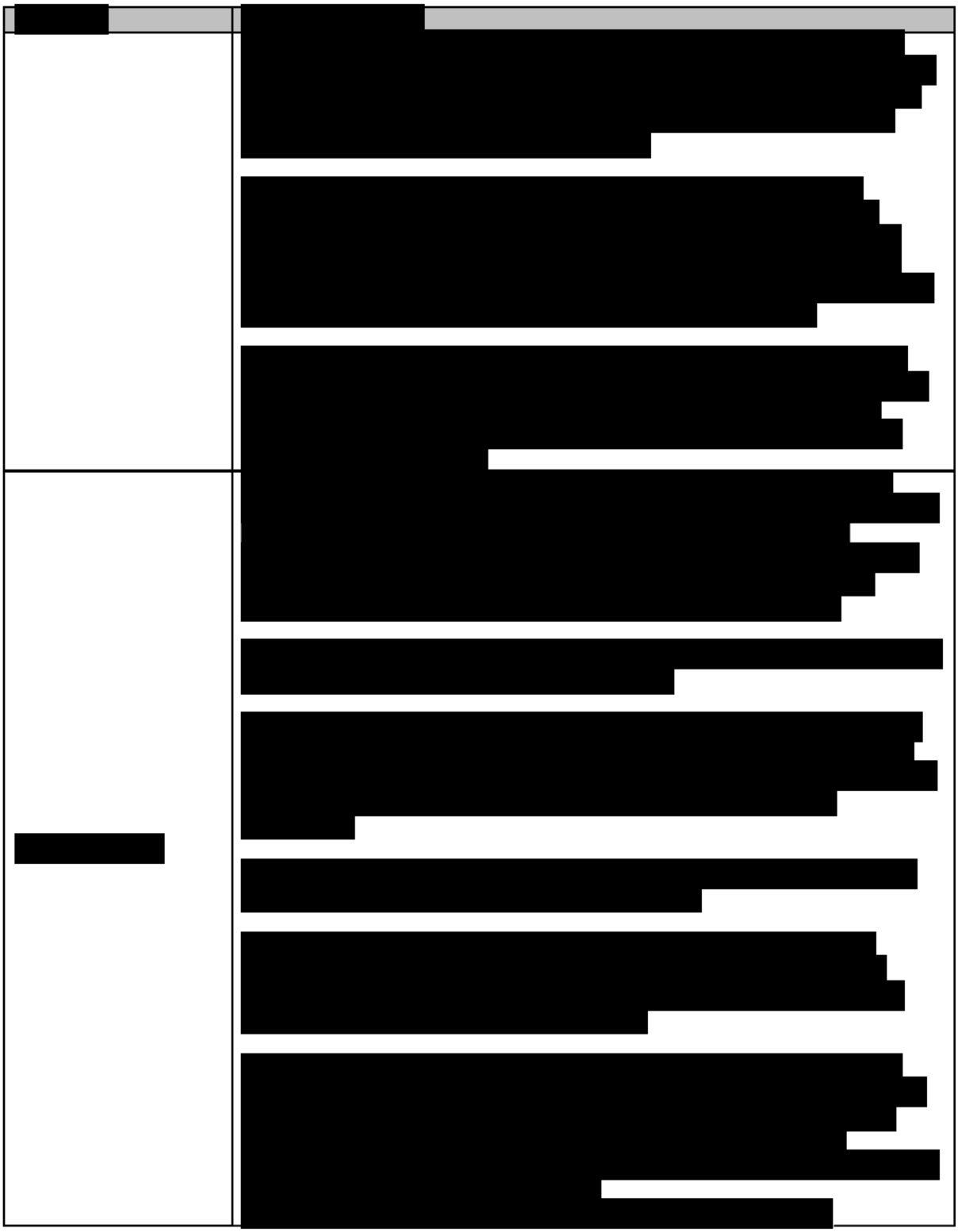


Clinical Investigation Plan

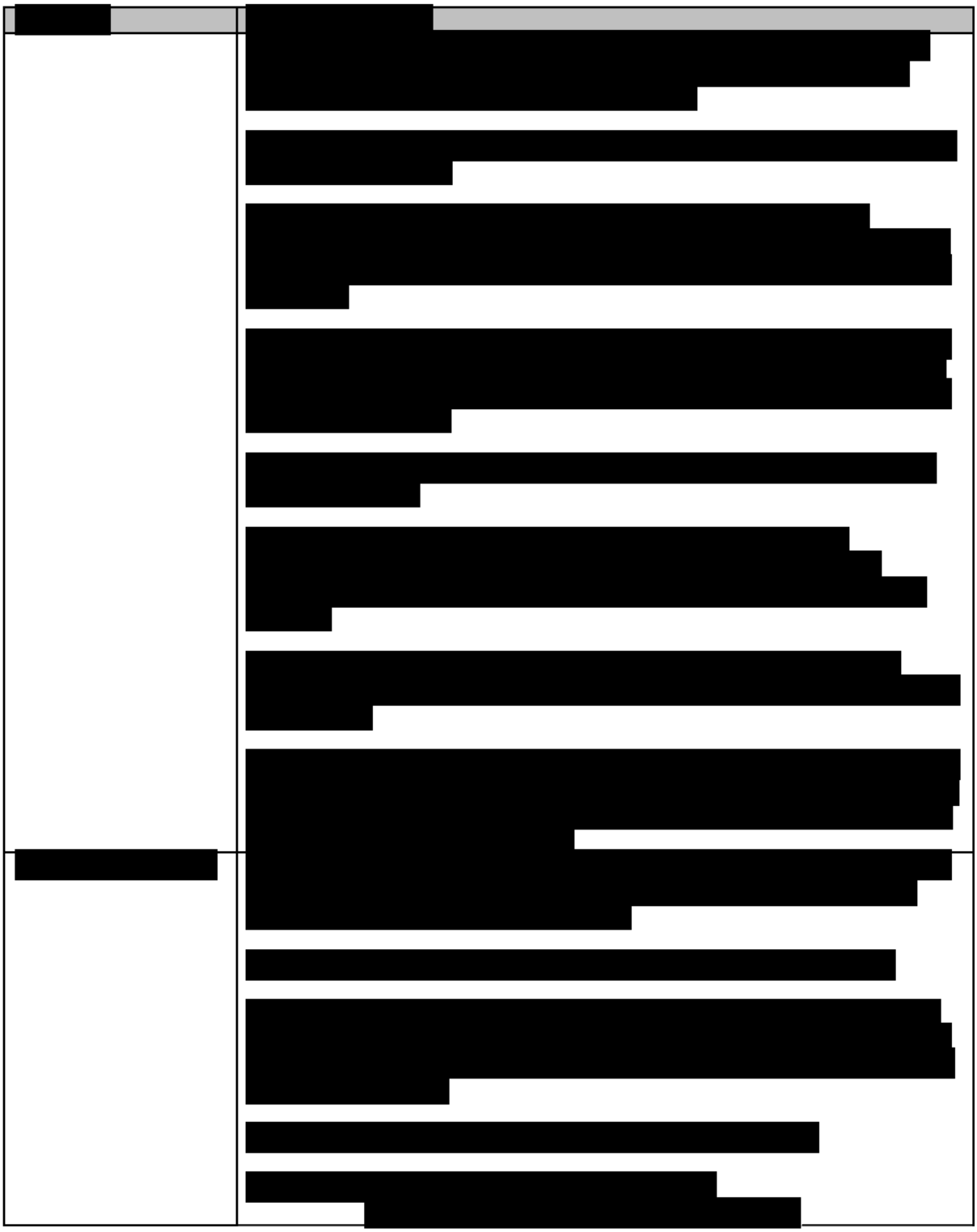


Clinical Investigation Plan

Clinical Investigation Plan



Clinical Investigation Plan



Clinical Investigation Plan

Table of Contents

Clinical Investigation Plan

2.0 Clinical Investigation Plan Synopsis

Title	A safety and effectiveness trial for a leadless pacemaker system – The LEADLESS II Study
Investigational Device	Nanostim™ Leadless Pacemaker (LP)
Regulatory Classification of the Investigational Device	Class III
Number of Institutions	Up to sixty sites worldwide with up to 50 investigation sites in the United States.
Number of Subjects	Up to 667. At least 50% of the subjects recruited from sites located in the United States.
Trial Population	Subjects who are at least 18 years old, and who are indicated for a VVI(R) pacemaker.
Schedule of Assessments	Enrollment, Implant, Pre-Discharge, 2-week, 6-week, 3-month, 6-month follow-up, and every 6 months thereafter until study completion. Subjects consent to continue in post-approval studies and will have follow-ups at one year and each year thereafter until seven years after implant.
Study Design	Prospective, non-randomized, single-arm, international multicenter, clinical safety and effectiveness investigation.
Study Objective	The primary objectives of this study are to evaluate the clinical safety and effectiveness of the Nanostim™ LP system in subjects who are indicated for VVI(R) pacemaker.
Primary Safety Endpoint	The primary safety endpoint evaluates the 6-month complication-free rate.
Primary Effectiveness Endpoint	The primary effectiveness endpoint evaluates pacing thresholds and R-wave amplitudes within the therapeutic range through 6 months post-implant.

Clinical Investigation Plan

Secondary Endpoint	The secondary endpoint evaluates an appropriate and proportional rate response during graded exercise testing (CAEP protocol), performed between 3-month and 6- month visit.
PMA Application	[redacted]
Study continuation and supplementary analyses after PMA application	[redacted]

Clinical Investigation Plan

Inclusion Criteria	Eligible subjects will meet **all** of the following: 1. Subject must have one of the clinical indications before device implant in adherence with Medicare, ACC/AHA/HRS/ESC single chamber pacing guidelines including: ☐ Chronic and/or permanent atrial fibrillation with 2 or 3° AV or bifascicular bundle branch block (BBB block), including slow ventricular rates (with or without medication) associated with atrial fibrillation; or ☐ Normal sinus rhythm with 2 or 3° AV or BBB block 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; and 2. Subject ≥18 years of age; and 3. Subject has life expectancy of at least one year; and 4. Subject is not enrolled in another clinical investigation; and 5. Subject is willing to comply with clinical investigation procedures and agrees to return for all required follow-up visits, tests, and exams; and 6. Subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent, approved by the IRB; and 7. Subject is not pregnant and does not plan to get pregnant during the course of the study.

Clinical Investigation Synopsis continued

Clinical Investigation Plan

Exclusion Criteria	Subjects will be excluded if they meet **any** of the following: 1. Subject has known pacemaker syndrome, has retrograde VA conduction or suffers a drop in arterial blood pressure with the onset of ventricular pacing; or 2. Subject is allergic or hypersensitive to <1 mg of dexamethasone sodium phosphate; or 3. Subject has a mechanical tricuspid valve prosthesis; or or 4. Subject has a pre-existing endocardial pacing or defibrillation leads; or 5. Subject has current implantation of either conventional or subcutaneous implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT); or 6. Subject has an implanted vena cava filter; or 7. Subject has evidence of thrombosis in one of the veins used for access during the procedure; or 8. Subject had recent cardiovascular or peripheral vascular surgery within 30 days of enrollment; or 9. Subject has an implanted leadless cardiac pacemaker.
Enrollment	Subjects who sign an IRB-approved informed consent and have an attempted or successful implant will be considered enrolled in the study.
Estimated Schedule	[redacted]
Continued Access Phases (CAP)	The CAP study will begin only after completion of enrollment of 667 patients in the IDE; the CAP cohort will follow the same schedule of evaluations as the IDE investigational plan except for the chronotropic assessment exercise protocol (CAEP) and the 24-hour Holter Monitor sub-studies. The maximum sample size for this IDE including CAP will be 1567.

Clinical Investigation Plan

Clinical Investigation Synopsis continued

Schedule of Assessments	<u>Pre-procedure Assessments</u> • Inclusion/exclusion criteria • Informed consent • Pregnancy assessment • 12-lead ECG • Medical history • Medications[1] <u>Implant Assessments</u> • Femoral vein assessment and access • Procedure details • Nanostim™ LP implant • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs <u>Post-procedure Assessments</u> • Access-site assessment • 12-lead ECG • X-ray of pacemaker • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs <u>2-week Visit</u> • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs

[1] Data are collected for beta blocker, ACE, ARB, anti-arrhythmic, anti-coagulant, and anti-platelet medications, at all visits.

Clinical Investigation Plan

Clinical Investigation Synopsis continued

Schedule of Assessments (continued)	<u>6-week Visit</u> • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs <u>3-month Visit</u> • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs • 24-hour Holter monitor with diary (30 subjects) • Graded exercise test (CAEP protocol) until 30 subjects provide data contributing to the analysis) <u>6-month Visit</u> • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs <u>Every 6-month Visits</u> • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs

Clinical Investigation Plan

Table 1: Schedule of Assessments

	Pre-procedure Assessments		Procedure Assessment	Post-procedure Assessments						
Activity	Screen & Enroll	Baseline	Implant	Post-procedure Assessment	2-week Follow-up Visit[1]	6-week Follow-up Visit[1]	3-month Follow-up Visit[2]	6-month Follow-up Visit[2]	Every 6-months until study completion[3]	Additional Visits
Inclusion Exclusion	✓									
Informed Consent	✓									
Pregnancy Assessment/Test	✓									
Medical History		✓								
Baseline Assessment		✓								
Procedure			✓							
Post-procedure Pre-discharge				✓						
Nanostim™ LP Assessment and Programming			✓	✓	✓	✓	✓	✓	✓	✓
12-lead ECG		✓		✓						
X-ray of a pacemaker				✓						
Follow-up Visit					✓	✓	✓	✓	✓	✓
24-hour Holter monitor with diary[4]							✓			
Graded exercise test CAEP Protocol[5]							✓			
EQ-5D patient survey				✓	✓	✓	✓			
Additional CRFs (when applicable)										
Adverse Event			✓	✓	✓	✓	✓	✓	✓	✓
Deviation		✓	✓	✓	✓	✓	✓	✓	✓	
Study Withdrawal				✓	✓	✓	✓	✓	✓	✓
Product Out of Service			✓	✓	✓	✓	✓	✓	✓	✓
System Revision				✓	✓	✓	✓	✓	✓	✓
Death			✓	✓	✓	✓	✓	✓	✓	✓
Healthcare Utilization				✓	✓	✓	✓	✓	✓	✓

1 ±7 days
2 ±30 days
3 ±45 days
4 All capable subjects are asked to wear a 24-hour Holter and complete a diary, until 30 subjects provide data contributing to the analysis. The preferred window to perform the 24 hour Holter test is between the 3-month and 6-month visit.
5 All capable subjects are asked to perform a CAEP treadmill test until 30 subjects provide data contributing to the analysis. The preferred window to perform the CAEP treadmill test is between the 3-month and 6-month visit.

3.0 Abbreviations

Abbreviation	Definition	Abbreviation	Definition
2°	Second degree	EP	Electrophysiology
3°	Third degree	ESC	European Society of Cardiology
ACC	American College of Cardiology	ICD	Implantable cardioverter defibrillator
ACT	Activated clotting time	IFU	Instructions for use
ADL	Activities of daily living	INR	International normalized ratio
AE	Adverse event	IRB	Independent or institutional review board
AHA	American Heart Association	LP	Leadless pacemaker
AV	Atrioventricular	MRI	Magnetic resonance imaging
BBB	Bifascicular bundle branch	PA	Pulmonary arterial
CAEP	Chronotropic assessment exercise protocol	PtIr	Platinum Iridium
CFR	Complication free rate	RR	Rate response
CIP	Clinical investigation plan (also referred to as clinical protocol)	RV	Right ventricular
CRF	Case report form	SAE	Serious adverse event
CRT	Cardiac resynchronization therapy	TiN	Titanium nitride
ECG	Electrocardiogram	UADE	Unanticipated adverse device effect

4.0 Introduction

Sponsor has developed a leadless pacemaker system (Nanostim™ LP) to eliminate leads, pockets, and connectors required by conventional pacemakers and to eliminate associated complications. This concept could improve patient comfort by replacing a surgical procedure with a percutaneous one, eliminating the visible lump and scar at a conventional pacemaker's pectoral implant site, and removing the need for activity restrictions to prevent dislodgement after implantation of a conventional lead. Finally, the concept could permit pacemaker patients to undergo magnetic resonance imaging (MRI) with specified machines, although this is not being evaluated under this protocol.

St. Jude Medical's Nanostim™ LP system consists of a pacemaker and its accessories: a programmer, introducer, delivery catheter, and retrieval catheters. The accessories are not intended for use alone or with any device other than the Nanostim™ LP. The pacemaker and all accessories, except the programmer, are single-use devices and are supplied sterile.

5.0 Purpose

The intent of this IDE study is to evaluate the safety and effectiveness of the implanted Nanostim™ LP for treatment of bradycardia. A Nanostim™ Programmer Link also investigational, will be used in conjunction with the Nanostim™ LP. The Nanostim™ Programmer Link is a programming device that when connected to the St. Jude Medical™ Merlin™ Patient Care System (Model 3650) allows the user to communicate with the Nanostim™ LP.

6.0 Clinical Protocol

6.1 Study Design and Scope

This is a prospective, non-randomized, multi-center, international clinical study designed to evaluate the safety and effectiveness of the Nanostim™ LP System in a subject population indicated for a VVI(R) pacemaker.

Sponsor will conduct the study at up to 60 centers worldwide with up to 50 centers in the United States. To meet study endpoints, the Sponsor expects to enroll up to 667 subjects [redacted] Sponsor will allow a maximum of 100 (15% of the total) enrollments per center [redacted] At least 50% of subjects will be recruited from sites located in the United States.

Enrollment in the LEADLESS II clinical study [redacted] All eligible subjects will undergo implant attempt with a Nanostim™ LP.

All subjects will consent to continue annual follow-ups each year until 7 years after implant, in a long-term post-approval study.

The following study evaluations will occur after implant:

- Pre-discharge assessment
- 2-week follow-up visit (in-office or clinic)
- 6-week follow-up visit (in-office or clinic)
- 3-month follow-up visit (in-office or clinic)
- 6-month follow-up visit (in-office or clinic)
- Every 6 months thereafter until study completion
- Subjects consent to continue in post-approval studies and will have follow-ups at one year and each year thereafter until seven years after implant.

Follow-up schedules will be calculated from the date of successful implant.

6.2 Study Objective and Endpoints

The primary objectives of this study are to assess the safety and effectiveness of the Nanostim device from implant through 6-months in a subject population indicated for a VVI(R) pacemaker.

Primary Safety Endpoint
The primary safety endpoint evaluates a 6-month complication-free rate based on CEC adjudication of the adverse event.

Primary Effectiveness Endpoint
The primary effectiveness endpoint evaluates pacing thresholds and R-wave amplitudes within the therapeutic range through 6 months post-implant.

Secondary Endpoint
The secondary effectiveness endpoint evaluates an appropriate and proportional rate response during graded exercise testing (CAEP protocol).

Supplementary Safety Endpoint
The supplementary safety endpoint evaluates a 1-year complication-free rate based on CEC adjudication of the adverse event.

[redacted]

Supplementary Effectiveness Endpoint

The supplementary effectiveness endpoint evaluates pacing thresholds and R-wave amplitudes within the therapeutic range through 1 year post-implant.

6.2.1 Primary Endpoints

[redacted]

6.2.1.1 Primary Safety Endpoint

The goal of the primary safety endpoint evaluation is to demonstrate an acceptable complication-free rate (CFR); including any complication that prevents initial implantation.

[redacted]

Subjects whose initial implantation procedure was not successful will not be eligible for re-implantation attempts with the investigational device at a later date.

Subjects who leave the study before their 6-month visit will be censored at the time they leave the study. So, any complications that occur in subjects that leave the study before their 6 month visit will be included in this analysis.

Primary Safety Endpoint Evaluation at 6 Months

H_0: CFR $\leq$ 86% vs. H_1: CFR > 86%

A sample size of 300 evaluable subjects [redacted] establishing a two-sided 95% confidence interval for CFR, with a lower bound exceeding 86%, based on an exact binomial distribution.

[redacted]

[redacted]

[redacted]

6.2.1.2 Primary Effectiveness Endpoint

The composite primary effectiveness endpoint will be used to evaluate pacing thresholds and R-wave amplitudes at the 6-month visit and to document the percentage of subjects with acceptable sensing and pacing performance. Pacing thresholds and R-wave amplitudes will be collected, tabulated for each visit, and also displayed as frequency plots. Acceptable ranges for sensing and pacing are shown in the table below.

Table 2: Acceptable Ranges for Sensing and Pacing

Parameter	Acceptable test values
Pacing voltage	Pacing threshold $\leq$ 2.0 V at 0.4 ms
R Sensitivity	R-wave amplitude $>$ 5.0 mV or $\geq$ value at implant

Success Criteria: A subject will be considered to have met the primary effectiveness endpoint if the pacing threshold voltage is $\leq$ 2.0 V at 0.4 ms **and** the sensed R-wave amplitude is either $\geq$ 5.0 mV at the 6-month visit or $\geq$ the value at implant.

[redacted]

[redacted]

[redacted]

The inability to sense or pace within the programmable range available in the Nanostim™ LP device, resulting in device repositioning, replacement, or removal will be captured in the associated safety endpoints.

Primary Effectiveness Endpoint Evaluation at 6 Months

H_0: Rate $\leq$ 85.0% vs. H_1: Rate > 85.0%

A sample size of 300 subjects [redacted] establishing a two-sided 95% confidence interval for conformance with the above-referenced criteria for pacing threshold and R-wave amplitude, with a lower bound exceeding 85.0%, based on an exact binomial distribution.

6.2.1.3 Data Analysis of Primary Safety and Effectiveness Endpoints

The following analysis populations are defined for the study:

Intent-to-Treat (ITT): [redacted]

Per Protocol (PP): [redacted]

The primary analysis population for the Primary Safety Endpoint will be the ITT population. The Primary Effectiveness Endpoint will be evaluated in both the ITT and PP populations.

[redacted]

All primary safety and effectiveness endpoints will be tested against the pre-specified performance goals at 6 months with exact, binomial tests.

[redacted]

[redacted]

[redacted]

[redacted]

6.2.1.4 Adaptive Sample Size Re-estimation

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2.1.6 Missing Data

All attempts will be made to ensure subject retention in the study to minimize the amount of missing data. Reasons for withdrawals will be documented and assessed relative to possible relationships to study primary endpoints.

[redacted]

6.2.1.7 Subgroup Analyses

[redacted]

6.2.1.8 Conditional Probability of Meeting 1-Year Primary Endpoints

[redacted]

[redacted]

[redacted]

6.2.2 Secondary Endpoint

The secondary endpoint includes evaluation of a CAEP exercise protocol. [redacted]

Secondary CAEP Endpoint

H_0: Mean Slope is Not Equivalent to 100%

$| \text{Slope} - 100\% | \geq \delta$

H_1: Mean Slope is Equivalent to 100%

$| \text{Slope} - 100\% | < \delta$

Where, δ = equivalence margin, equal to 35%

CAEP exercise protocol
All capable subjects will be asked to perform a maximal effort CAEP exercise protocol to demonstrate an appropriate and proportional response of sensor-indicated rate in graded exercise tests.
Data from subjects unable to complete at least stage 3 of the exercise protocol (3.6 METS) will be excluded from the analysis, although their results will still be reported. Thirty subjects will provide data contributing to the analysis. [redacted].

The analysis of these exercise test data will provide an estimate of the slope of the normalized increase in sensor-indicated rate versus normalized CAEP workload for each subject. An analysis of these data will also estimate the 95% confidence interval for the mean slope across subjects, which has a pre-specified success criterion requiring that this confidence interval must fall between slopes of 65% and 135%. [redacted]

[2] [redacted]

[redacted]

[redacted]

For each subject (i), a slope will be estimated using data points (Yij) on Xij, where j= individual paired values for subject (i). The estimate of the slope for data from subject (i) is given by:

$$Slope_i = \Sigma (X_{ij}) (Y_{ij}) / \Sigma (X_{ij})^2$$

Where, the summations are across individual paired values (j) for subject (i) taken at the end of every completed CAEP stage. The mean slope (SlopeMean) is estimated by the average slope across N subjects:

$$SlopeMean = \Sigma Slope_i / N$$

Where the summation is over i = 1, ..., N, with N equal to the number of subjects.

The standard error of the mean slope is estimated in the usual manner:

$$SE(SlopeMean) = [\Sigma (Slope_i - SlopeMean)^2 / N(N-1)]^{1/2}$$

The test statistic for evaluation of the CAEP endpoint becomes:

$$Test\ Statistic = [\ |\ SlopeMean - 100\%\ |\ -\ 35\%\ ]\ /\ SE$$

[redacted]

(SlopeMean)

The boundary of the critical zone for the above test statistic is equal to $[- t_{0.025, N-1}]$, associated with a one-sided Student's t-test, an alpha value equal to 0.025, and (N-1) degrees of freedom.

The CAEP test will be performed any time after the beginning of the 3-month visit window [redacted]

6.2.3 Supplementary Endpoints

The following supplementary endpoints will be evaluated at 12 months after implant.

6.2.3.1 Supplementary Safety Endpoint Evaluation at 12 Months

H_0: CFR $\leq$ 84.5% vs. H_1: CFR > 84.5%

A sample size of 600 evaluable subjects [redacted] establishing a two-sided 95% confidence interval for CFR, with a lower bound exceeding 84.5%, based on an exact binomial distribution.

Subjects who leave the study before their 1 year visit will be censored at the time they leave the study. Therefore, any complications occurring in subjects who depart the study prior to their 1 year visit will be included in this analysis.

Based on the above assumptions, the total enrollment is expected to be 667 subjects, [redacted]

Successful demonstration of an 86 % CFR at six months does not preclude 84.5 % CFR at one year.

6.2.3.2 Supplementary Effectiveness Endpoint Evaluation at 12 Months

H_0: Rate $\leq$ 85.0% vs. H_1: Rate > 85.0%

A sample size of 600 subjects [redacted] establishing a two-sided 95% confidence interval for successful sensing and pacing, with a lower bound exceeding 85.0%, based on an exact binomial distribution.

The inability to sense or pace within the programmable range available in the Nanostim device, resulting in device repositioning, replacement, or removal will also be captured in the associated safety endpoints.

6.2.3.3 Data Analysis of Supplementary Safety and Effectiveness Endpoints

The supplementary safety and effectiveness endpoints must be met at the 1-year evaluations, [redacted] All supplementary safety and effectiveness endpoints will be tested against the pre-specified performance goals at 12 months with exact binomial tests.

6.2.4 Additional data

The following additional data will be recorded and reported:

- All adverse events, and whether or not each is device-related or procedure-related
- Implant success rate and reasons for unsuccessful implant
- Device handling characteristics at implant
- Number of device repositioning at time of implantation
- Implant duration, fluoro duration, and time from implant to hospital discharge
- Final LP placement
- Demographics: gender, age, ethnicity, race, indication for pacemaker implant
- Medical history
- Use of beta blocker, ACE, ARB, anti-coagulation, anti-arrhythmic, and anti-platelet medications
- A table and histogram across all subjects of remaining longevity at the six-month and 1-year visits, as displayed by the programmer based on delivered therapy, programmed settings, percent pacing, and measured pacing impedance. Average pacing rate, impedance, pulse amplitude, pulse duration and percentage pacing will also be reported for all visits.
- Hospitalizations
- Mortality

Holters

All capable subjects will be asked to wear a 24-hour Holter monitor and complete a diary, until 30 subjects provide data contributing to the analysis. [redacted]

[redacted]

6.2.5 Definitions used in LEADLESS II study

Adverse Event: Any unfavorable clinical event which impacts, or has the potential to impact the health or safety of a subject caused by or associated with a study device or intervention.

Complication: A device- or procedure-related serious adverse event, including any adverse event that prevents initial implantation.

Cardiac Tamponade: Confirmed or suspected accumulation of fluid in the pericardial space.

Cardiac Perforation: An excursion of the Nanostim™ LP through the cardiac muscle. Signs and symptoms of a perforation by Nanostim™ LP may include radiographic evidence of excursion of the LP into the pericardial sac, abnormal echocardiography indicative of a perforation, the accumulation of fluid in the pericardium, cardiac tamponade, or subject symptoms such as chest pain and discomfort.

Device-malfunction: the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

[redacted]

Diaphragmatic/Phrenic Nerve Stimulation: Electrical activation of the diaphragm muscle by the device output pulse. The abrupt diaphragmatic contraction is noted clinically as hiccups associated with each pacing stimulus. The pacing stimulus may stimulate the diaphragm either directly or indirectly via the phrenic nerve.

Dislodgement: The movement of the Nanostim™ LP from its originally implanted position resulting in elevated pacing thresholds or a decrease in sensing.

Elevated Pacing Thresholds: Pacing thresholds > 2.5 V at 0.4 ms at implant. Following lead maturation at 6-8 weeks, an increase in pacing thresholds of 1.2 V at 0.4 ms or greater between visits. This definition is intended to serve as a guideline and it is understood that individual subjects may have unique situations.

Implant procedure duration: Defined as the time from delivery catheter and Nanostim™ LP insertion to removal.

Implant success rate: Defined as the number of subjects leaving the implant procedure with an implanted and functioning Nanostim™ LP device, divided by the number of subjects in whom implantation is attempted.

Loss of Capture: The inability of the device's output pulse to result in depolarization and contraction of the ventricle. Causes include insufficient stimulus strength, separation of the electrode from the myocardium and placement of the stimulating electrode in contact with a non-responsive portion of the myocardium such as scar tissue. Delivery of an output pulse at a time when the myocardium is physiologically refractory is not loss of capture, since capture is not physiologically feasible.

Loss of Sensing: A condition in which the pulse generator is unable to sense intrinsic cardiac signals.

Oversensing: The detection of inappropriate electrical signals by the pulse generator's sense amplifier. These signals, such as myopotentials, electromagnetic interference, or T waves must be of sufficient duration to interfere with normal device function.

Procedure duration: Defined as the time from 18F femoral introducer insertion to removal.

Serious Adverse Event (SAE): Any untoward medical occurrence that:

a. Led to death,
b. Led to serious deterioration in the health of the subject, that either resulted in
    1. A life-threatening illness or injury, or
    2. A permanent impairment of a body structure or a body function, or
    3. In-patient or prolonged hospitalization, or

4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or requires an invasive strategy to remedy, or

c. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Sponsor understands that the following items meet the definition of serious adverse event if they require hospitalization or prolong hospitalization, even though an invasive approach may not be necessary to resolve: AV fistula, pseudoaneurysm, blood transfusions, tricuspid valve damage, pericardial effusion, pulmonary embolus, device dislodgement, right ventricular perforation, thrombus formation on the device, ventricular arrhythmias even if not associated with an invasive strategy to remedy.

Non-invasive means such as device re-programming do not meet the criteria for medical or surgical intervention.

Time to discharge: Defined as the time from introducer sheath removal to discharge.

Unanticipated adverse device effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. [21 CFR 812.3(s)]

Unavoidable adverse event: An unavoidable AE is defined as an adverse event related to the implant procedure that is expected to occur for a projected duration in all subjects.

Undersensing: The failure of the pulse generator to sense R-waves, causing delivery of inappropriately timed, asynchronous or competitive output pulses. Undersensing can sometimes be corrected by programming the device to a more sensitive setting, i.e., decreasing the millivolt value.

6.3 Subject Selection

The inclusion and exclusion criteria are consistent with recommendations of the European Society of Cardiology,[1] American College of Cardiology, American Heart Association, and the Heart Rhythm Society.[2] Additionally, sponsor has included investigator input.

Eligibility for implant is based on conformance to all prospectively defined inclusion and exclusion criteria.

6.3.1 Inclusion Criteria

Eligible subjects will meet **all** of the following.

1. Subject must have one of the clinical indications before device implant in adherence with Medicare, ACC/AHA/HRS/ESC single chamber pacing guidelines including:
   - ☐ Chronic and/or permanent atrial fibrillation with 2 or 3° AV or bifascicular bundle branch block (BBB block), including slow ventricular rates (with or without medication) associated with atrial fibrillation; or
   - ☐ Normal sinus rhythm with 2 or 3° AV or BBB block 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; and
2. Subject is ≥18 years of age; and
3. Subject has a life expectancy of at least one year; and
4. Subject is not be enrolled in another clinical investigation; and
5. Subject is willing to comply with clinical investigation procedures and agrees to return for all required follow-up visits, tests, and exams; and
6. Subject has been informed of the nature of the study, agrees to its provisions and has provided a signed written informed consent, approved by the IRB; and
7. Subject is not pregnant and does not plan to get pregnant during the course of the study.

6.3.2 Exclusion Criteria

Subjects will be excluded if they meet **any** of the following.

1. Subject has known pacemaker syndrome, has retrograde VA conduction, or suffers a drop in arterial blood pressure with the onset of ventricular pacing; or
2. Subject is allergic or hypersensitive to < 1 mg of dexamethasone sodium phosphate (DSP);
3. Subject has a mechanical tricuspid valve prosthesis; or
4. Subject has a pre-existing endocardial pacing or defibrillation leads; or
5. Subject has current implantation of either conventional or subcutaneous implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) device; or
6. Subject has an implanted vena cava filter; or
7. Subject has evidence of thrombosis in one of the veins used for access during the procedure; or
8. *Subject had recent cardiovascular or peripheral vascular surgery within 30 days of enrollment; or
9. Subject has an implanted leadless cardiac pacemaker

*Recent cardiovascular or peripheral vascular surgery within 30 days of enrollment is defined as the following:

- **Percutaneous valvular correction ≤30 days**
- **Femoral or abdominal vascular procedure involving incisional access ≤30 days**
- **Peripheral arterial endovascular procedure or surgery ≤30 days**
- **Cardiac surgery ≤72 hrs 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**

6.4. Study Procedures

This section provides a description of all the clinical-investigation-related procedures that subjects undergo during the clinical investigation. **Figure 1** illustrates study flow and **Table 1** lists a summary of scheduled assessments. Refer to **Figure 1** and **Table 1** for an overview of the required study procedures at each interval or study visit.

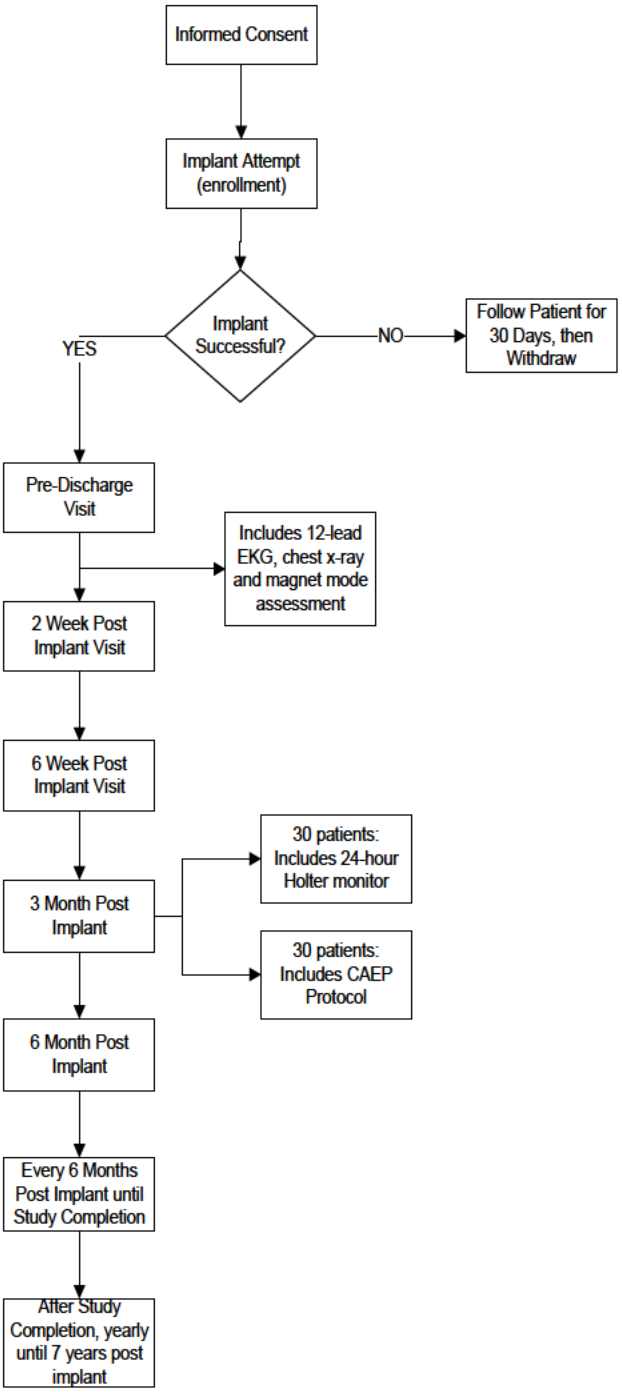
The clinical-investigation-related procedures do not require additional radiation compared to a traditional VVIR lead implant and conform to standard of care for pacemaker patient management with the exception of the following:

- Femoral vein access instead of subclavian vein access
- Addition of Treadmill tests
- Addition of 24 hour Holter monitor

Sponsor representatives may assist the investigator in assessing pacemaker effectiveness (for example pacing, sensing, and rate response effectiveness), downloading diagnostic information and programming pacemaker parameters. Sponsor representatives may also assist the team in equipment setup prior to and during a procedure.

Clinical Investigation Plan

Figure 1: Study Flow Diagram



6.4.1 Enrollment Requirements

6.4.1.1 Recruitment and Enrollment

Candidates for this clinical investigation include patients indicated for a VVI(R) pacemaker. Pre-enrollment records will include evidence of diagnosis indicating need for VVI(R) pacemaker. For the Leadless II study, it is the sponsor's intention that the enrolled subject population be as representative as possible of the eligible population. Physician investigators are strongly encouraged to evaluate all consecutive eligible subjects for participation in the study and, if inclusion and exclusion criteria are met, to approach all eligible subjects, regardless of gender. Centers will be selected for participation in the study based on their ability to screen and enroll eligible subjects, and perform the required study procedures. [redacted]

Screen subjects as outlined by the inclusion/exclusion criteria. Obtain informed consent from the subject. Collect data on the subject, including gender, age, ethnicity, race, cardiac disease history, cardiac medications (beta blockers, ACE, ARB, anti-platelets, anti-arrhythmics, anti-coagulants), arrhythmia history, and indication for pacemaker implant. Subjects who sign an IRB-approved informed consent and have an attempted or successful implant will be considered enrolled in the study.

Once eligibility screening is completed, subject provides informed consent, and the investigator implants the Nanostim™ LP—or attempts to implant—complete and submit the forms listed under the Implant Procedures to sponsor.

6.4.1.2 Subject Numbering

An identification (ID) number will identify enrolled subjects. The format of this ID number is a combination of the study number, subject number assigned by SJM and a subject ID assigned by the site.

6.4.2 Baseline Assessment

Investigator will record subject's medical history on the Enrollment Form. Investigator will record specific cardiac medications (beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics) given to the subject during the same hospital stay as the procedure, as well as during the follow-up period. All subjects will undergo standard laboratory assessment per site's standard of care. For female subjects of childbearing age, investigator will document a pregnancy assessment, which may include a obtaining a blood sample for conducting a pregnancy test.

[redacted]

Investigator will not start any study-specific procedures or alterations of patient care until the informed consent process has been completed and investigator obtains a signed Informed Consent Form.

6.4.2.1 Medications

Investigator will administer all medications per hospital standard of care for pacemaker implant and femoral venous catheterization procedures. Use of anticoagulation medications is not required with the implantation of the Nanostim™ LP. Investigator will record beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics given during procedure.

6.4.3 Implant Procedure

6.4.3.1 Femoral Vein Assessment and Access

Turi (2005, 2008), Abu-Fadel *et al* (2009), Seto *et al* (2010), and Fitts *et al* (2008) have shown that physicians can minimize access-site complications by using ultrasound guidance or fluoroscopic guidance when accessing vessels in the groin.[3-7] Although sponsor supports using either technique for assessing femoral vein access-site location, size and presence of disease, investigator will use medical judgment and follow institutional standard of care when accessing the femoral vein during catheter-based procedures.

The ideal puncture site should be located **below the inguinal ligament and above the bifurcation** (Refer to Figure 2).[5,8-10] Penetrate the skin and puncture the femoral vein using the Seldinger technique. Due to the introducer sheath size, investigator may need to "nick and spread" the tissue at the access-site location to allow for easier transition of the introducer sheath through the tissue tract.

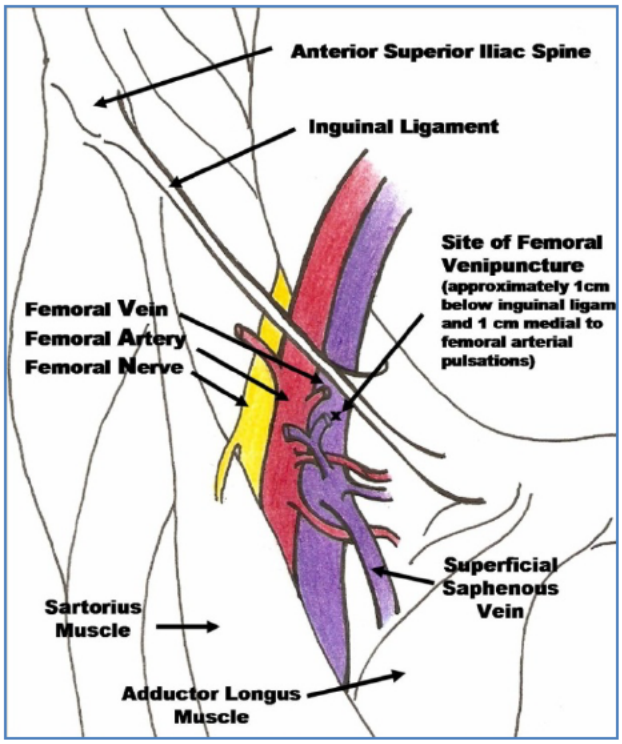


Figure 2. Location of femoral vein in relation to femoral artery, inguinal ligament and femoral head

6.4.3.2 Nanostim™ LP Preparation and Implant

Investigator will prepare and implant the Nanostim™ LP in accordance with the manufacturer's instructions for use (IFU). Consult the IFU for implantation guidelines and general handling information. Only approved investigators will be responsible for performing the implant procedure, including placement of the Nanostim™ LP. Investigator will follow standard institutional catheter-based and pacemaker-lead implantation procedures, guidelines, and precautions.

6.4.3.3 Nanostim™ LP Assessment and Programming

Investigator and/or sponsor will interrogate the Nanostim™ LP using the market-approved St. Jude Medical™ Merlin™ Patient Care System (Model 3650) with the Nanostim™ Programmer Link. Investigator will measure and record the following parameters.

- Capture threshold at (0.4 msec)*
- Impedance*
- R-wave amplitude*
- Battery voltage and Estimated time to RRT
- Cumulative paced and sensed event counters

* *R-wave amplitude measurements are not required if the subject's intrinsic rate has been established to be below 30 beats per minute. Capture thresholds are not required if a high*

ventricular rate is present. Confirm at least three consecutive beats have capture before recording the capture threshold results.

** For subjects implanted with the Nanostim™ LP (Model S1DLCP)-Impedance measurements should not be done because performing this commanded measurement in a device with a high resistance battery can render the device immediately non-functional.*

To avoid potential complications associated with under-sensing, Investigator shall program a sensing margin of at least two times the intrinsic cardiac amplitude (e.g., for an intrinsic R-wave of 4 mV, program the R-sensitivity ≤2 mV).

To avoid potential complications associated with loss of pacing capture, Investigator shall maintain pulse amplitude margin of at least two times the pacing threshold (e.g., for a pacing threshold of 0.5V, program the pulse amplitude ≥1.0V).

6.4.3.4 Nanostim™ LP Repositioning and/or Release

Once the investigator implants the Nanostim™ LP and successfully demonstrates acute effectiveness, the investigator may release the Nanostim™ LP. Investigator may reposition Nanostim™ LP, if necessary. For release and repositioning procedures, refer to the IFU. Once the Nanostim™ LP has been released, investigator will use a retrieval catheter for removal, if needed (Refer to Retrieval Catheter IFU). Once the Nanostim™ LP has been removed, investigator may attempt to implant another Nanostim™ LP, or instead, choose to implant a market-approved pacemaker or ICD. When the investigator has released the Nanostim™ LP, s/he will use fluoroscopy to assess positioning of the implanted Nanostim™ LP.

6.4.3.5 Unsuccessful Implant

Investigators will follow subjects who have an unsuccessful implant for a period of 30 days to evaluate for adverse events. At the end of the 30 days, the investigator will withdraw the subject. The investigator must document the nature of the unsuccessful implant on the Implant Form.

Data Submission

Once information has been collected and required testing has been completed at the implant visit, complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Enrollment Form (includes medications)
- Implant Form (includes medications)
- Nanostim™ LP Assessment and Programming Form
- Study Withdrawal Form, if applicable

- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Death Form, if applicable
- Product Out of Service Form, if applicable

6.4.4 Nanostim™ LP Retrievals and Replacement

When considering Nanostim™ LP retrieval and replacement, investigators will refer to the respective IFUs.

Under normal operating conditions, the Nanostim™ LP battery is expected to last for approximately 8 years. In the event a Nanostim™ LP must be removed during the clinical study follow-up period, investigators may opt to replace LPs in the following ways:

- Retrieve the first Nanostim™ LP and implant a new Nanostim™ LP,
- Deactivate the first Nanostim™ LP and implant a second Nanostim™ LP in close proximity to the first one, or
- Deactivate the first Nanostim™ LP and implant a traditional pacemaker or ICD with a lead.

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- System Revision Form
- Healthcare Utilization Form
- Nanostim™ LP Assessment and Programming Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Death Form, if applicable
- Study Withdrawal Form, if applicable
- Product out of Service Form, if applicable

*If the subject has the Nanostim™LP removed at any time during the study, and the subject **will not** receive a replacement Nanostim™LP, follow the subject for 30 days, and withdraw the subject from the study. Complete and submit the following case report forms to St. Jude Medical, Sylmar, CA using the EDC system.*

- Study Withdrawal Form
- Product Out of Service Form

- Nanostim™ LP Assessment and Programming Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Death Form, if applicable

6.4.5 Post-procedure Assessments

The follow-up period is sufficient to demonstrate safety and effectiveness. Additionally, during this 6-month follow-up period, sponsor will identify any residual risks and complications.

Subjects will be seen at the following intervals:

- Pre-discharge assessment
- 2-week follow-up visit (in-office or clinic)
- 6-week follow-up visit (in-office or clinic)
- 3-months follow-up visit (in-office or clinic)
- 6-months follow-up visit (in-office or clinic)
- After completing 6-month follow-up assessment, subjects will return every 6 months until study completion
- Subjects consent to continue in post-approval studies and will have follow-ups at one year and each year thereafter until seven years after implant.

Table 3: Follow-up Assessment Windows

Post Implant (Pre-Discharge)	**2-week follow-up**	**6-week follow-up**
0-2days	14 ± 7 days	42 ± 7 days
3-month follow-up	**6-month follow-up**	
90 ± 30 days	180 ± 30 days	
Every 6 months post 1-year until study completion		
Every 180 ± 45 days		

6.4.5.1 Access-site Management During Hospital Stay

Investigator will manage vascular-access sites per standard of care. Investigator will assess and document any post-procedural access-site bleeding event based on the following grading system.

ACCESS-SITE OOZING: Superficial bleeding of a cutaneous or subcutaneous origin characterized by diffuse localized bleeding and controlled with minimal care (e.g., application of manual pressure, application of sandbag).

ACCESS-SITE HEMATOMA: A localized collection of extravasated blood in subcutaneous tissue at the access site that does not require intervention. A metric ruler should be used to measure the widest portion of the hematoma.

ACCESS-SITE HEMATOMA REQUIRING INTERVENTION: A localized collection of extravasated blood in subcutaneous tissue at the access site that is considered life threatening and requires emergency wound exploration (e.g., acutely expanding hematoma, acute leg pain/numbness/swelling) and/or prolongation of hospital stay.

ACCESS-SITE RE-BLEEDING: Localized bleeding at the access site that occurs after hospital discharge. These bleeds are typically associated with an event (e.g., fall, attempted suture removal, physical activity).

6.4.5.2 Pre-Discharge Assessment

Investigator will assess all subjects at the implant center prior to hospital discharge, or within 2-days post implant, whichever is shorter. Investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics ;
- Measure and record Nanostim™ LP performance, as described in 6.4.3.3 Nanostim™ LP Assessment and Programming;
- Assess magnet mode;
- Program Nanostim™ LP per physician discretion;
- Obtain a 12-lead electrocardiogram (ECG) with pacing ON;
- Obtain a posterior/anterior (P/A) and lateral view chest x-ray to assess final LP position;
- Investigator will use medical judgment and provide institutional standard of care for post-pacemaker-implant monitoring.
- Collect medical billing information for implant (i.e. UB04 billing form)

Data Submission
Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Pre-Discharge Form (includes medication changes)
- Nanostim™ LP Assessment and Programming Form
- EQ-5D patient survey
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable

6.4.5.3 2-week and 6-week follow-up visits

All subjects will return to the investigation site for a 14-day and 42-day (±7 days) follow-up visit. During this visit, investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics ;
- Measure and record LP performance, as described in 6.4.3.3 Nanostim™ LP Assessment and Programming;
- Program Nanostim™ LP and adjust programmable parameters of Nanostim™ LP, as needed.

Data Submission
Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Nanostim™ LP Assessment and Programming Form
- EQ-5D patient survey
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable

- Death Form, if applicable
- Healthcare Utilization Form, if applicable

6.4.5.4 3-Month Visit

All subjects will return to the investigation site for a 90-day (±30 days) follow-up visit. During this visit, investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics ;
- Measure and record Nanostim™ LP performance, as described in 6.4.3.3 Nanostim™ LP Assessment and Programming;
- Program Nanostim™ LP and adjust programmable parameters of Nanostim™ LP, as needed;
- Holter Data Collection[3]
    - Connect each capable subject to 24-hour Holter monitor (until 30 subjects contribute to the analysis); set Nanostim™ LP to **VVIR** mode, if indicated (This test may be performed between 3 and 6 months post-implant).
- CAEP Protocol[4]
    - Administer CAEP protocol (until 30 subjects contribute to the analysis); with rate-response feature in **VVIR ON** mode (refer to CAEP protocol – this test may be performed between 3 and 6 months post-implant).
    - After completing CAEP protocol, program Nanostim™ LP and adjust programmable parameters of Nanostim™ LP, as needed.

Data Submission

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Nanostim™ LP Assessment and Programming Form
- EQ-5D patient survey
- Medications, if any changes
- Study Withdrawal Form, if applicable

[3] Holter data collection can be done any time between the 3-month and 6-month follow-up visit.
[4] Administration of the CAEP protocol can be done any time between the 3-month and 6-month follow-up visit, (until 30 subjects contribute to the analysis).

- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Graded Exercise Test Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable

6.4.5.5 6-Month Follow-up Visit

All subjects will return to the investigation site for a 180-day (±30 days) follow-up visit. During this visit, investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics ;
- Measure and record Nanostim™ LP performance, as described in 6.4.3.3 Nanostim™ LP Assessment and Programming.

Data Submission

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Nanostim™ LP Assessment and Programming Form
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable

6.4.5.6 Follow-up Visit Every Subsequent 6-Months until Study Completion

All subjects will return to the investigation site every 180-days (±45 days) follow-up visit. During this visit, investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics ;
- Measure and record Nanostim™ LP performance, as described in 6.4.3.3 Nanostim™ LP Assessment and Programming;
- Program Nanostim™ LP and adjust programmable parameters of Nanostim™ LP, as needed.

Data Submission
Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Nanostim™ LP Assessment and Programming Form
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable

6.4.5.7 Unscheduled Follow-up Visits

If a subject returns to the investigational site for a visit that is related to the device or implant procedure, the research team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics;
- As applicable, measure and record Nanostim™ LP performance, as described in 6.4.3.3 Nanostim™ LP Assessment and Programming;
- Program Nanostim™ LP and adjust programmable parameters of Nanostim™ LP, as needed.

Data Submission
Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Nanostim™ LP Assessment and Programming Form

- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable

7.0 Hospitalizations

All hospitalizations, outpatient services, emergency room and urgent care visits that are related to heart failure, cardiac/ non-cardiac reasons and Nanostim™ LP implant/retrieval/replacement procedure(s) must be reported to St. Jude Medical via a Healthcare Utilization Form within 10 working days of the center becoming aware of the subject's admission to the hospital. The investigation team will submit the Healthcare Utilization Form and supporting documentation (i.e., Admission/Discharge Summary) to St. Jude Medical, Sylmar, CA using the EDC system. The UB04 billing record will be required for hospitalizations and emergency room visits that are cardiac related.

8.0 Protocol Deviations

Investigators are required to adhere to the investigation plan, signed Investigator's Agreement, applicable federal or state/local, laws and regulations, and any conditions required by the IRB, or FDA.

A protocol deviation is used to describe situations in which the investigation plan was not followed. Investigator must report all deviations from the investigational to sponsor per 21 CFR §812.150. In addition, investigator must report all deviations to the reviewing IRB per the IRB's reporting requirements.

Investigator must notify sponsor and the reviewing IRB of any deviation from the investigation plan to protect the life or physical well-being of a subject in an emergency as soon as possible, but not later than 5-working days after the deviation has occurred, or no later than 5-working days after the investigator becomes aware of the deviation.

9.0 Adverse Events

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

A Clinical Events Committee (CEC) will review and adjudicate all Adverse Events. The CEC will base their final adjudication on the information provided on the case report forms, medical records, and their clinical knowledge and experience.

Investigator will document all AEs on the Adverse Event Form, including (at a minimum) a description of the event, date of onset, relationship to the investigational device, required interventions, duration, and outcome. Investigator will monitor all AEs until they are resolved, determined to be a chronic condition or the subject is lost to follow-up. Investigator will report all AEs regardless of whether it is anticipated or unanticipated and regardless of classification, seriousness, outcome or causality.

Should an AE occur, complete an Adverse Event Form and submit to sponsor. If an adverse event occurs between scheduled visits, report the event as soon as possible without waiting until the next scheduled visit. Report the adverse event to the IRB/MEC per the IRB/MEC policy. Investigator will return any retrieved devices to sponsor for analysis.

Serious Adverse Event (SAE) Reporting
The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined herein.

The date the site staff became aware of the event that met the criteria of an SAE, it must be recorded in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

Unavoidable AEs are not reportable unless the condition worsens or continues beyond the time frame listed below. Unavoidable AEs, listed below, do not need to be reported if they are resolved within the time frame specified.

Table 4: Unavoidable AEs related to the Implant Procedure

Event	Time Frame post-Implant
Anesthesia related nausea/vomiting	<24 hours
Low-grade fever (<100 degree Fahrenheit fever or < 37.8 degree Celsius	< 48 hours
Percutaneous access pain	< 72 hours
Mild to moderate bruising/ecchymosis at percutaneous access site	< 72 hours
Sleep problems (insomnia)	< 72 hours
Back pain related to laying on the table	< 72 hours

If an **UNANTICIPATED ADVERSE DEVICE EFFECT** occurs, Sponsor requires the investigator to report any UADE to the Sponsor as soon as possible [21 CFR 812.150 (a) (1)], but within 3 calendar days [Sponsor's requirement] of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB/MECs per IRB/MEC requirements. Sponsor will take any steps necessary to investigate the event, and will be responsible for notifying FDA and all other participating IRBs/MECs and investigators.

Should sponsor determine, either through physician reports or in-house testing, that an unanticipated adverse event presents an unreasonable risk to participating subjects, sponsor will suspend the clinical investigation and notify all participating investigators, IRBs/MECs and FDA.

Sponsor will provide to FDA on a quarterly basis an interim safety and adverse event report.

Table 5: List of foreseeable adverse events and anticipated adverse device effects

*Access site bleeding event	
Air embolism	Induced ventricular ectopy or arrhythmias
Angina pectoris	Infection, local at access site, or systemic
Arterial puncture	Insufficient cardiac output
AV fistula	Intermittent capture
Bladder puncture	Interruption of desired pacemaker function due to electrical interference, either electromyogenic or electromagnetic
Blood transfusion	Keloid formation
Blunted or poor sensor response	Loss of normal device function due to battery failure or component malfunction
Body rejection phenomena	Muscle and nerve stimulation
Bowel penetration	Myocardial damage
Cardiac arrhythmias	Myocardial infarction
Cardiac dissection	Myocardial irritability
Cardiac perforation	Oversensing
Cardiac tamponade	Pacemaker syndrome
Chronic nerve damage	Palpitations
Damage to vessels	Pericardial effusion or rub
Death	Pericarditis
Device dislodgment	Phrenic nerve/diaphragmatic stimulation
Dizziness	Pneumothorax
Dyspnea	Premature battery depletion
Embolism	Programmer/software anomaly
Endocarditis	Pseudoaneurysm formation
Excessive Bleeding	Psoas abscess
Exit block	Reaction to contrast
Failure to capture/loss of capture	Septic arthritis
Femoral nerve injury with resulting paresthesias	Seroma
Heart Failure	Syncope
Hematoma formation, including retroperitoneal hematoma/hemorrhage	Threshold elevation
High impedance	Thromboemboli

Inability to interrogate or program due to programmer or device malfunction	Thrombosis

Table 5: List of foreseeable adverse events and anticipated adverse device effects (continued)

Undersensing	Venous perforation
Valve damage	Ventricular ectopy
Venous occlusion	Ventricular tachycardia

*Access site bleeding event is defined in section 6.4.5.1.

A right ventriculogram carries risk, most notably, allergic reaction to contrast media.

10.0 Deaths

All subject deaths that occur during this study must be reported to St. Jude Medical within 3 calendar days of the center being notified (Refer to SAE Reporting in Section 9).. Notification of a death should include a detailed statement of the pertinent events and be signed by the investigator in addition to the completion of the appropriate forms (Death form, Withdrawal form, and Product Out of Service form) and submitted to St. Jude Medical, Sylmar, CA using the EDC system. It is the investigator's responsibility to notify the IRB per the IRB policy.

- Date and time of death
- Place death occurred (e.g. hospital, nursing home, subject's home)
- If death was witnessed
- Identification of the rhythm at the time of death, if known (include any available documentation)
- Cause of death
- Any other circumstances surrounding the death
- Approximate time interval to death from the initiating event
- Autopsy report (if performed)
- Whether it was device and/or procedure related
- Whether it was related to the study

If any of the above information is not available, investigator will provide an explanation in the death narrative of what attempts (and how many) were made to obtain the information, and the outcome of those attempts. At a minimum, investigator will place two (2) phone calls, followed by a certified letter, to the subject's next of kin and provide clinical notes and witness statements. If possible, interrogate the pacemaker. Retrieve and print all episode diagnostics, and programmed parameters. If applicable, the pacemaker

should then be programmed **OFF.** Attempt to explant the pacemaker and return any explanted devices to sponsor for analysis promptly. Clearly state on Case Report Form the reason the pacemaker is not being returned to sponsor.

11.0 Committees and Core Laboratories

11.1 Data and safety monitoring board (DSMB)

Sponsor will establish an independent DSMB to review safety data. The DSMB will consist of at least 3 members with study-related backgrounds. Members will include at least one statistician and two cardiologists with pacemaker experience. St. Jude Medical will appoint members of the DSMB and the chairperson. St. Jude Medical may provide administrative support to DSMB meetings, but will not be a voting member and will not be present during closed portions of the meeting. Non-DSMB members are not allowed to be present during DSMB closed meetings. Refer to DSMB Charter, RC-02447.

Sponsor will provide to FDA within 10 working days of receipt copies of written communication from the DSMB that relates to safety concerns, or changes to the study plan, procedures or informed consent document. Sponsor will provide the DSMB within 10 working days copies of any letter from FDA that relates to safety concerns, or changes to the study plan, procedures or informed consent document.

11.2 Clinical events committee (CEC)

Sponsor will establish an independent CEC to review all adverse events. The CEC's role is to determine relationship of event to device and or procedure. The CEC will consist of at least 3 members with study-related backgrounds. Members will include cardiologists with pacemaker experience. St. Jude Medical will appoint members of the CEC and the chairperson. St. Jude Medical may supply study information and provide administrative support for CEC meetings, but will not be a voting member. Refer to CEC Charter, RC-02470.

11.3 Holter core laboratory

Sponsor will establish an independent core laboratory to review all 24-hour Holter monitors. The core laboratory's role is to evaluate and report Holter findings.

12.0 Withdrawals

Withdrawal is defined as termination of a subject's participation from the clinical trial. All reasonable efforts should be made to retain the subject in the clinical trial until

completion of the clinical trial. All reasons for withdrawal will be documented. Reasons for withdrawal include, but are not limited to the following:

- Subject Death
- Subject and/or Family Request representing withdrawal of consent
- Subject Lost to Follow-Up: Subject will be considered "lost to follow-up" after a minimum of 2 documented phone calls by personnel at the investigational center to the subject or emergency contact, a certified letter is sent to the last known address and two consecutive visits pass without the investigator receiving data.
- Subject Participation terminated by investigator based on the best medical interest of the study subject
- Nanostim™ LP explanted and not reimplanted
- Unsuccessful Implant.

A Withdrawal Form will be completed and submitted to St. Jude Medical, Sylmar, CA using the EDC system.

13.0 Risk Analysis

St. Jude Medical addresses the risk of poor usability of the programmer through a usability engineering process complying with EN 62366:2007.

St. Jude Medical has implemented a risk management process in conformance with EN ISO 14971:2012. The application of this risk management process to the leadless pacemaker system is documented in a risk management file. The risk management file also includes a risk management plan (St. Jude Medical's standard operating procedure for risk management).
This risk management process includes risk analysis, risk evaluation, and risk control. These are documented for the leadless pacemaker system in a top-down system hazard analysis; bottom-up failure mode effects analyses for the pacemaker, catheters, programmer and introducer; software safety analyses for the pacemaker and programmer; annual reviews of post-production information on similar devices; and a system risk management report. These bottom-up analyses provide risk analysis for single component failure as required by EN 45502-1:1997 §19.3.

13.1 Product-related risks

St. Jude Medical conducted system hazard analysis for the Nanostim™ LP system. This analysis found that the system employed state of the art therapy and materials. Failure-mode-effects analyses of each device in the system confirmed that the level of risk is as expected for pacing systems. Thus, the risk assessment focused on the potential influence of novel design features: implantation procedure; access site; fixation characteristics; absence of lead, connector, and antenna; device retrieval; and

conductive communication with Nanostim™ programmer Link. St. Jude Medical's risk assessment identified uncertainties relating to product-specific risks, such as those associated with percutaneous delivery via a femoral vein, and dislodgement or migration. The need for product-specific risk-control measures was identified, such as fixation optimization and warning of risk for subjects with pulmonary arterial hypertension or lung disease.

13.2 Clinical risks

St. Jude Medical's risk assessment following the system hazard analysis concluded that the subject population and delivered therapy are essentially the same as those of existing VVIR therapy. Thus, existing clinical evidence addresses proof of concept of therapy and supports the view that clinical risks should be the same as those seen with comparable existing products.
The follow-up period of 6-12 months is consistent with the follow-up duration of comparable devices in studies for regulatory approval, which in turn was determined by the well-known maturation time of the interface between the electrode and myocardium, which is typically reached by three months[5].
Animal study, human clinical trial results and feedback from physicians indicate that the delivery, implantation and retrieval procedures will not expose the subject, the physician or third parties to radiation in excess to that from implantation of a conventional single chamber pacemaker and lead.

13.3 Anticipated clinical benefits

Implantation of the Nanostim™ LP for cardiac pacing could offer certain advantages as compared to a conventional pacemaker. Specifically, the benefits that are associated with the use of the Nanostim™ LP could include:

- Precise and repeatable procedure;
- Percutaneous procedure (potential outpatient procedure);
- Eliminates the need for lead (no risk of lead fracture, lowers risk of infection);
- Eliminates the need for a pocket (lowers risk of infection, no need for scar and/or lump);
- Eliminates the need for connectors (eliminates connector complications);
- Eliminates the visible lump and scar at a conventional pacemaker's pectoral implant site;
- Could lessen the need for activity restrictions after implantation;

[5] Hayes DL, Friedman PA., Cardiac pacing, defibrillation, and resynchronization: a clinical approach, Wiley 2011,

13.4 Benefit/risk assessment

It is concluded from preclinical data (risk analysis and literature review) that clinical risks are comparable to those associated with currently available therapy. Uncertainty exists in relation to risks associated with novel features (percutaneous delivery via a femoral vein and the possibility dislodgement or migration). These residual risks cannot be estimated with confidence without data from a clinical investigation. Taking into account the nature of the possible harm that could arise from these device-related risks and the assurance provided by pre-clinical data, the risk-benefit balance associated with the use of the Nanostim™ LP in a clinical trial is considered to be favourable.

13.5 Conclusions from pre-clinical risk evaluation

Clinical investigation needs to confirm safety and performance of novel design features. The basis for design of this investigation may be summarized as follows:

- Most design features are equivalent to existing products and will have been verified by pre-clinical evaluation.
- Literature shows that for conventional pacemakers, approximately 96% of subjects are event-free at 6-months.
- Risk analysis indicates novel features should not be associated with significant residual risks or complications.
- It is not possible to design a clinical investigation to investigate low-level or unexpected risks, on the basis of a statistical analysis.
- The objective should be to identify a flaw in the pre-clinical risk analysis, exposing the minimum number of subjects to the risk.

It is concluded that the results of the pre-clinical evaluation justify the design of the clinical investigation to determine whether the Nanostim™ LP is suitable for the purpose and the population for which it is intended. The clinical investigation has been designed to ensure that the results obtained have clinical relevance and scientific validity, and address the clinical investigation objectives.

14.0 Description of Device

14.1 Identification of the device: proprietary and code names

The Nanostim™ leadless pacemaker system consists of these items:

System Model#	Device Identifier/Model	Device Name	Description
S1DLCP*	N/A	Nanostim Leadless Pacemaker Nanostim Delivery System Catheter	Includes Nanostim Leadless Pacemaker built with old Battery assembled with Gen 1.5 Delivery System Catheter
LSS10201	LSP102	Nanostim Leadless Pacemaker	Includes Nanostim Leadless Pacemaker built with new Battery assembled with Gen 1.5 Delivery System Catheter
	LSCD101	Nanostim Delivery System Catheter	
LSS10202	LSP102	Nanostim Leadless Pacemaker	Includes Nanostim Leadless Pacemaker built with new Battery assembled with Gen 1.6 Delivery System Catheter
	LSCD102	Nanostim Delivery System Catheter	
N/A	S1RTRI	Nanostim Retrieval Catheter	System 1, Triple Loop Retrieval Catheter for retrieving a Nanostim Leadless Pacemaker
N/A	S1RSIN	Nanostim Retrieval Catheter – Single Loop Snare	System 1, Single Loop Retrieval Catheter for retrieving a Nanostim Leadless Pacemaker
N/A	S1S18F	Nanostim Introducer Kit	System 1, 18F Introducer Kit, 30cm
N/A	LSN18501	Nanostim Introducer Kit	18 French Introducer Kit, 50 cm
N/A	S1LINK	Nanostim Programmer Link	System 1, Programmer Link and Accessories For interrogating and programming the pacemaker after implant

*Note: the Nanostim Leadless Pacemaker, model S1DLCP is no longer being distributed or implanted. However, patients implanted with this device are continued to be followed using

this protocol and SJM recommendations outlined in the communication to investigators dated October 28, 2016. This device is now being replaced with pacemaker Model LSP102.

REF	Name in sponsor' product lifecycle management system	Name on labels on the device and its packaging	Notes	Acronym
S1DLCP	System 1, leadless cardiac pacemaker	Nanostim™ Leadless Pacemaker	Includes pacemaker and catheter for delivering the pacemaker	LP
S1LINK	System 1, communications link for SJM Merlin programmer	Nanostim™ Programmer Link	For interrogating and programming the pacemaker after implant	PRG
S1S18F	System 1, 18 French introducer, 30 cm length	Nanostim™ Introducer Kit	For use with pacemaker, delivery catheter, or retrieval catheters	INT
LSN18501	System 1, 18 French introducer, 50 cm length	Nanostim™ Introducer Kit	For use with pacemaker, delivery catheter, or retrieval catheters	INT
S1RSIN	System 1, single-loop retrieval catheter	Nanostim™ Retrieval Catheter - Single Loop Snare	For retrieving an implanted pacemaker with a single-loop snare	RET
S1RTRI	System 1, tri-loop retrieval catheter	Nanostim™ Retrieval Catheter - Triple Loop Snare	For retrieving an implanted pacemaker with a tri-loop snare	RET

14.2 Description of the device and its intended application

The Nanostim™ LP system consists of the Nanostim™ LP and its accessories listed in §13.1.

The intended application of the Nanostim™ LP is implant in the right ventricle, with permanent duration (greater than 30 days). The intended application of the delivery catheter, retrieval catheters, and introducer is external communicating, circulating blood contact, with limited duration (less than 24 hours). The intended application of the communications link is external, with skin contact via an approved cable and ECG electrodes.

The devices in the system achieve their intended purposes as described in the subsections below:

14.2.1 Nanostim™ LP

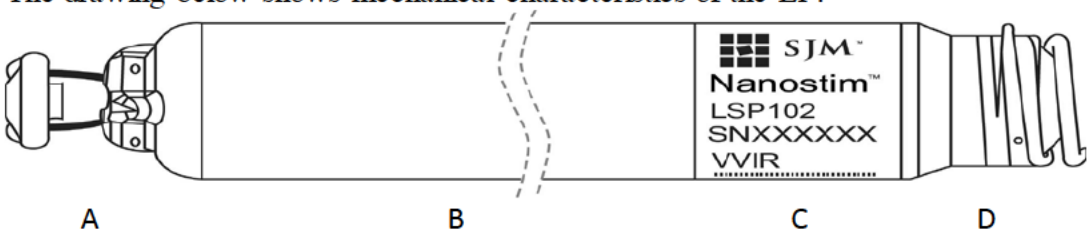
The Nanostim™ LP provides bradycardia pacing as a pulse generator with built-in battery and electrodes, for permanent implantation in the apex of the right ventricle. As a leadless pacemaker, it does not need a connector, pacing lead, or pulse generator pocket. A distal non-retractable, single-turn helix 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 tip electrode is a titanium-nitride coated platinum-iridium disc located at the center of the fixation helix, with a geometric surface area of 2 mm^2. The tip electrode includes 0.1 to 0.7 mg of dexamethasone sodium phosphate, intended to reduce inflammation. The ring electrode is the uncoated part of the titanium pacemaker case, with a geometric surface area >500 mm2. The inter-electrode distance is >10 mm. The maximum depth of penetration of the fixation mechanism in tissue is 1.3 mm. The pacemaker's proximal end has a feature for docking to delivery and retrieval catheters, which provides for repositioning capability.

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.

Otherwise, the Nanostim™ LP has the same operating principles as a conventional cardiac pacemaker. For further information refer to tthe Instructions for useof the device.

The drawing below shows mechanical characteristics of the LP.



A. Docking Interface button with cables	B. Ring electrode	C. Insulated Nosecone
D. MP35N fixation helix	E. Titanium nitride (TiN) coated platinum-iridium (PtIr) electrode with steroid (proximal to helix).	

Pacemaker length = 42 mm.
Pacemaker outer diameter (max) = 6.15 mm.

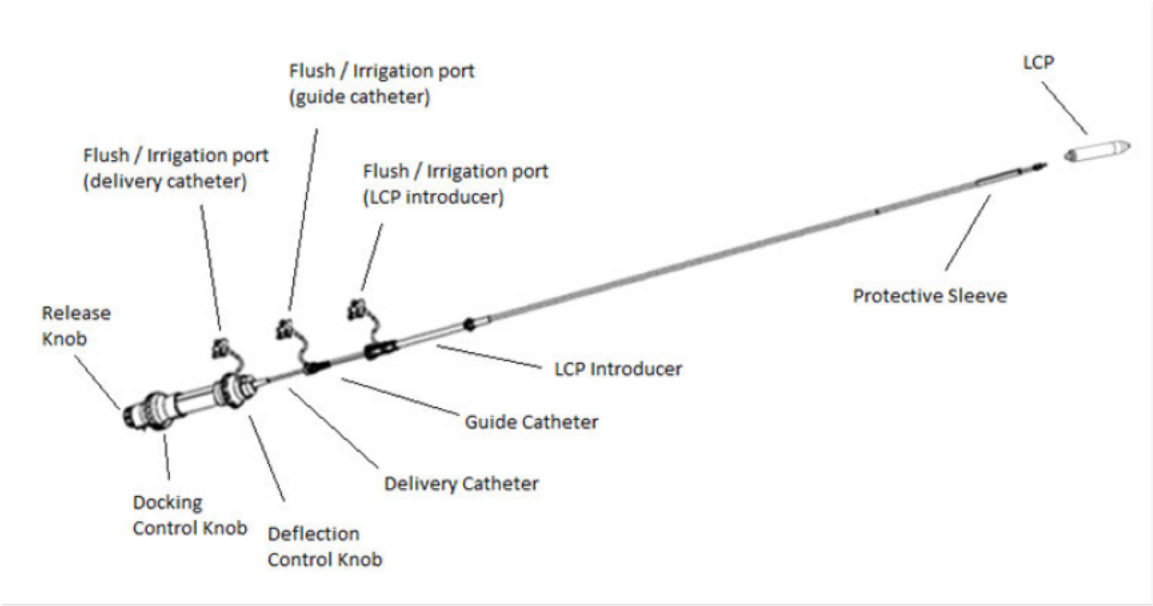
14.2.2 Delivery catheter

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 apex of 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 Nanostim™ LP 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. The system includes an introducer, a steerable delivery catheter, and an integrated guiding catheter with a protective sleeve designed to protect the fixation helix and electrode. The catheter has an effective length of 128cm and the catheter maximum outer diameter is 4.5 mm (0.178 inch). The Nanostim Delivery System Catheter, Model LSCD101 contains a 10F steerable delivery catheter while the Nanostim Delivery System Catheter, Model LSCD102 contains a 9F steerable delivery catheter.

The drawing below shows mechanical characteristics of the delivery catheter:



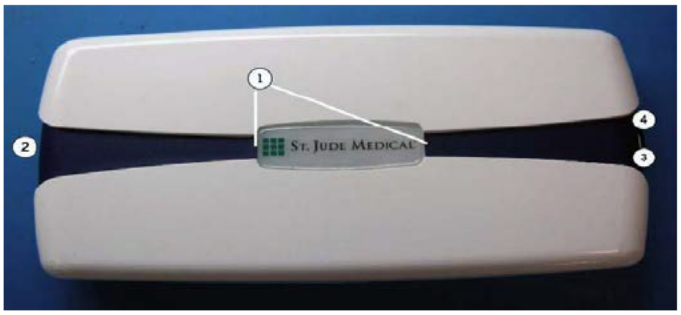
14.2.3 Nanostim™ Programmer Link

The programmer displays the patient's electrocardiogram and the status of the implanted Nanostim™ LP, and it sends commands to change Nanostim™ LP parameter settings as directed by a user. The programmer transmits signals to an implanted LCP via conducted communication with subliminal 250 kHz pulses applied to the skin electrodes. Apart from this conducted communication, it has the same operating principle as a conventional pacemaker programmer.

The Nanostim™ Programmer Link uses a St. Jude Medical Merlin Patient Care System Programmer (Model 3650) with a USB interface to an external module (Nanostim™ Programmer Link). The module uploads St. Jude Medical 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. For further information refer to DC-01471, Instructions for use, S1LINK programmer.

Clinical Investigation Plan

The photographs below show mechanical characteristics of the Nanostim™ Programmer Link:



Top view

1. LED lights will illuminate when the S1LINK is receiving appropriate power
2. Patient connector. Connect to the patient using the patient cable and skin electrodes.
3. USB connector. Connect to the St. Jude Merlin programmer using the USB cable.
4. Auxiliary power connector. Not required in normal use

Bottom view

1. The mating slot in the middle of the S1LINK is designed to slide on top of a mount that is affixed via glue to the back of a St Jude Merlin programmer.
2. The S1LINK is approximately 4.5" x 9.5" x 1.5". Its case is made of plastic. The S1LINK weighs approximately one pound.

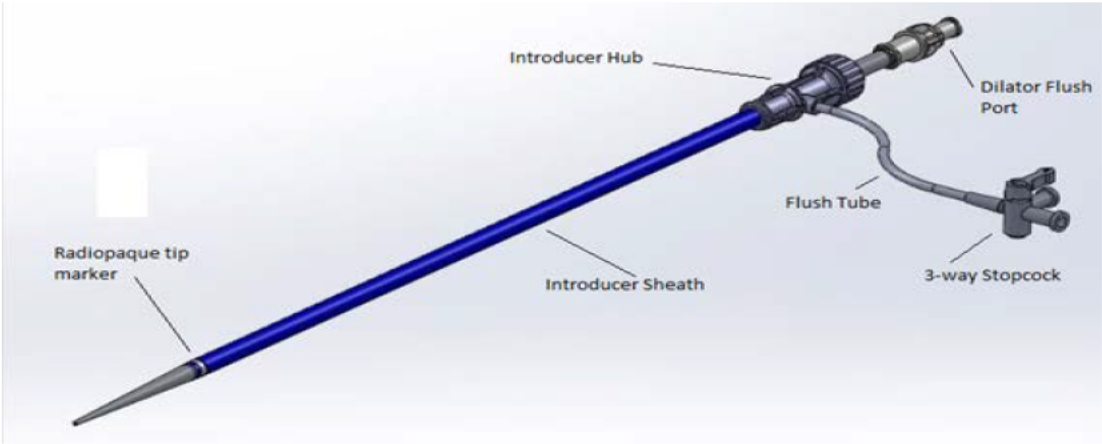
14.2.4 Nanostim™ 18F introducer kit

The system includes an 18F introducer kit intended to provide a conduit into the venous system for insertion of diagnostic and other interventional devices. The Introducer Kit is comprised of a dilator and an introducer sheath. The Introducer Kit is compatible with 0.035" and 0.038" guidewires and is available in 18F and two lengths, 30cm (model S1S18F) or 50cm (model LSN18501).

The introducer sheath is fitted with a hemostasis valve to prevent blood loss and minimize air introduction during introducer insertion and/or exchange. A sideport with a three-way stopcock is provided for fluid infusion. The introducer features a radiopaque tip marker incorporated within the sheath material to identify the location of the distal tip of the sheath. For further information, refer to the device instructions for use.

Clinical Investigation Plan

The drawings below show mechanical characteristics of the 18F introducer kit:



1. Introducer Sheath
2. Dilator

Model	S1S18F	LSN18501
Length	30 cm (11.8 inches)	50 cm (19.7 inches)
Inner Diameter (ID)	6.4 mm (.252 inches)	6.4 mm (.252 inches)

14.2.5 Nanostim™ Retrieval catheters

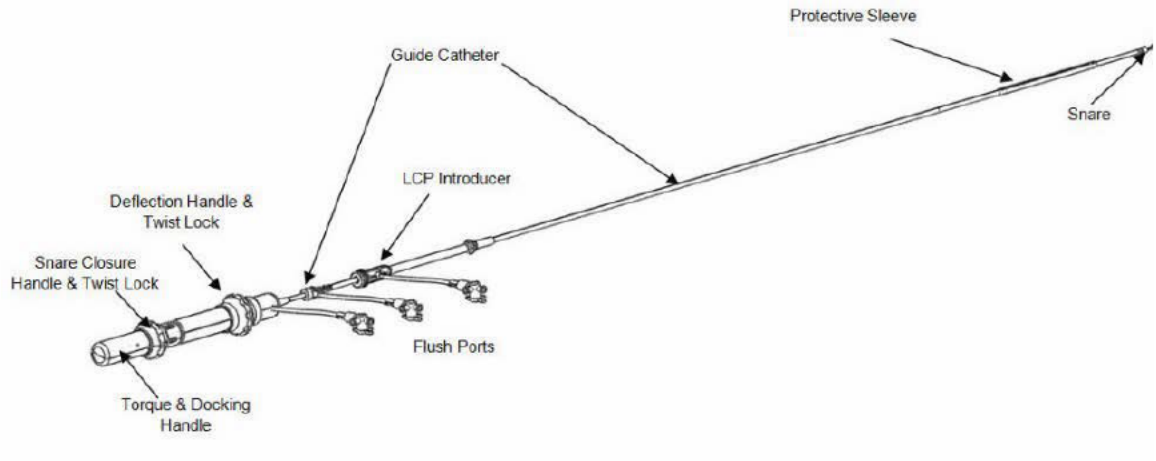
The retrieval catheters use a snare to engage the docking feature on the proximal end of the Nanostim™ LP, mate the retrieval catheter with the docking cap, unscrew it, and retrieve it.

Consequently, the retrieval catheter provides means for a single operator to:

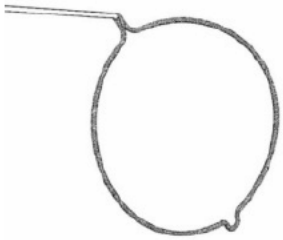
- Mate with the proximal button of the Nanostim™ LP from an access site in the groin through the femoral vein to the right ventricle.
- Dock to the Nanostim™ LP,
- Rotate the Nanostim™ LP to unscrew the helix from the endocardium,
- Protect the Nanostim™ LP helix and electrode during retrieval
- Extract 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). For additional information, refer to the device Instructions for use.

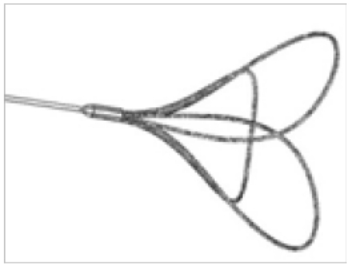
The drawings below show mechanical characteristics of the Retrieval catheter system



Catheter effective length = 128 cm, catheter outer diameter (max) = 4.5 mm (0.176 inch).



Single-loop snare for S1RSIN
Loop inner diameter = 19 mm (0.748 inch)



Triple-loop snare for S1RTRI
Loop inner diameter = 20 mm (0.787 inch)

14.3 Configurations and Variants

In this clinical investigation, St. Jude Medical includes two variants each of the leadless pacemaker[6] and delivery catheter, and two variants of the retrieval catheter. St. Jude Medical may incorporate a validated change to the Nanostim™ LP implant and/or programmer software, when necessary, to correct observed non-conformance with intended device operation.

[6] Note: the pacemaker, model S1DLCP is no longer being distributed or implanted. However, patients implanted with this device are continued to be followed using this protocol and SJM recommendations outlined in the communication to investigators dated October 28, 2016.

15.0 Investigator Information

This clinical investigation will be conducted by investigators with experience and/or willingness to be trained in the use of the device therapy for the treatment of bradyarrhythmias. An investigator should have experience in and/or will be responsible for:

- Conducting the clinical investigation in accordance with the signed agreement with sponsor, the investigation plan, all applicable FDA regulations (21 CFR Parts 50, 54, 56, 812), GCP guidelines, and any conditions of approval imposed by the IRB/MEC
- Providing signed Investigator's Agreement, RC-02445
- Providing signed Financial Disclosure Form
- Providing IRB/MEC-approved Informed Consent
- Collection and archiving of data obtained pursuant to the requirements of the investigation plan during the course of the study and after the study has been completed
- Strict adherence to the investigation plan testing requirements
- Screening and selecting appropriate subjects.

It is acceptable for the principal investigator to delegate one or more of the above functions to an associate or co-investigator, however, the principal investigator remains responsible for the proper conduct of the clinical investigation, complying with the investigation plan and collecting all required data. In clinical investigations involving active implantation of an investigational product, the investigation is not transferable to other implant centers attended by the investigator unless prior approval is obtained from sponsor.

16.0 Monitoring Procedures

St. Jude Medical will serve as the sponsor of the LEADLESS II clinical investigation. It is the responsibility of St. Jude Medical as the sponsor of the study to ensure proper monitoring of the investigation and to see that all the clinical requirements are met.

Prior to beginning the study, sponsor personnel will contact the investigator or designee to discuss the investigation plan and to review the data requirements in detail. A monitor will visit the investigator or designee periodically during the study to monitor progress, to assist in gathering the required data and to answer any questions. During these visits, the clinical monitor will review the subject's records to verify that all records and files are up to date, and to assure compliance with all requirements of the protocol and FDA regulations.

The investigator will make subject and study records available to the clinical monitor for periodic inspection.
Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

Responsibility for overall study management will be held by the DVP, Global Clinical Affairs, St. Jude Medical.

Clinical Studies Department
St. Jude Medical
15900 Valley View Court
Sylmar, CA 91342
TEL: +1 (818) 493-3297
FAX: +1 (800) 254-6411

16.1 FDA Inspections

The investigator and/or designee should contact sponsor within 24 hours upon being notified of an impending FDA inspection. A clinical monitor may assist and review study documentation with the investigator and/or designee to prepare for the audit.

An investigator shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where investigational devices are used and to inspect and copy all records relating to an investigation.

An investigator shall permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

17.0 Labeling

Sponsor will provide all implants and accessories with labels in USA stating, **"CAUTION--Investigational device. "Limited by Federal (or United States) law to investigational use."** Sponsor will also provide implants and accessories for use in Canada with appropriate Canadian labeling.

Sponsor will provide all implants and catheters as sterile units, and the packaging lists the method of sterilization, manufacturing date, manufacturer name and address, use before date, that devices are single use only, model number, and lot or serial number.

The programmer and accessories' labels contain the company name, location and phone number, model number, and lot or serial number.

Software versions are displayed on the programmer screen and in printed or saved reports. Validated changes to implant and programmer software are allowed during the study, when necessary, to correct an observed nonconformance with intended device operation.

Nanostim implants, catheters and programmers will be stored in a clean, dry, secure location at room temperature prior to shipment to the clinical site.

18.0 Consent Materials

All subjects will be consented for seven-year follow-up, so that they can additionally contribute to post-approval studies. Refer to sample consent form, Patient Informed Consent, RC-02444.

Failure to obtain informed consent from a subject prior to study enrollment should be reported to sponsor within 5 working days and to the reviewing IRB consistent with the IRB's reporting requirements.

19.0 IRB Information

IRB approval for the study and informed consent will be required prior to beginning the study. A copy of the IRB approval and corresponding informed consent must be forwarded to sponsor prior to authorization of the institution to begin the study. Any withdrawal of IRB approval should be reported to sponsor within 5 working days of the withdrawal of approval.

A list of IRBs for Institutions participating in the clinical investigation will be provided upon request.

20.0 Other Institutions

The name and address of each institution, at which a part of the investigation may be conducted, that has not been identified under IRB information, will be provided upon request.

21.0 Records and Reports

Clinical investigators are required to maintain all study records, prepare and submit reports, and permit FDA Bioresearch Monitoring Inspections relating to the investigator's participation in and conduct of the study, as described in 21 CFR §812.150. Sponsor will provide study data to the FDA on an annual basis or as requested by the FDA. Sponsor

will provide to FDA on a quarterly basis an interim safety and adverse event report. Sponsor will provide an IDE interim report to FDA within one month of completion of the 30th subject Holter monitor.

21.1 Custody

An investigator may withdraw from the responsibility to maintain records for the period required and transfer custody of the records to any other person who will accept responsibility for them as described, including the requirements regarding FDA inspection. Notice of transfer shall be given to sponsor and FDA no later than ten working days after transfer occurs.

21.2 Retention Period

Investigator is required to maintain records during the investigation and for a period of two years after the date on which the investigation is terminated or completed. Sponsor will maintain records until they are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

22.0 Publications

This study will be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

23.0 Appendices

23.1 Appendix A: Graded Exercise Test (CAEP Protocol)

The Chronotropic Assessment Exercise Protocol (CAEP)

Stage	Speed (MPH)	Grade (%)	Time (min)	Cumulative time	METs
0	1.0	0	2	2	1.5
1	1.0	2	2	4	2.0
2	1.5	3	2	6	2.8
3	2.0	4	2	8	3.6
4	2.5	5	2	10	4.6
5	3.0	6	2	12	5.8
6	3.5	8	2	14	7.5
7	4.0	10	2	16	9.6
8	5.0	10	2	18	12.1
9	6.0	10	2	20	14.3
10	7.0	10	2	22	16.5
11	7.0	15	2	24	19.0

Source:
Wilkoff, B. L., Corey J., "A Mathematical Model of the Cardiac Chronotropic Response to Exercise", Journal of Electrophysiology, 3(3) June 1989, pages 176-180

24.0 Bibliography

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