A feasibility study to evaluate the effect of concomitant renal denervation and cardiac ablation on AF recurrence

Clinical Investigation Plan (CIP)

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Clinical Investigation Plan Signature Page

Study Title: A feasibility study to evaluate the effect of concomitant renal denervation and cardiac ablation on AF recurrence

SJM CPRB Code: **CR-13-026-GE-RD**

Protocol ID: **SJM-CIP-0009**

Study Devices: EnligHTN™ Renal Denervation System

St Jude Medical Cardiac Ablation 'Toolkit' including: Cool Path Duo/Safire Blu Duo Ablation Catheter or Cool Flex Ablation Catheter, EnSite Velocity System, Agilis NxT

I have read and agree to adhere to the Clinical Investigational Plan and all regulatory requirements applicable in conducting this clinical study. I will provide copies of this clinical investigational plan and all pertinent information to study personnel and will discuss this information with them and ensure they are fully informed regarding the device and the conduct of the study according to other applicable regulations, to applicable laws.

_____

Site Principal Investigator Name (please print)

_____ _____

Site Principal Investigator Signature Date

Table of Contents

1 Synopsis

Title:	A feasibility study to evaluate the effect of concomitant renal denervation and cardiac ablation on AF recurrence
Acronym:	RDN + AF
Purpose:	The purpose of this post market clinical investigation is to complete preliminary evaluation on whether or not concomitant renal denervation with the EnligHTN™ Renal Denervation System and cardiac ablation will result in improved outcomes as compared to ablation alone in patients with uncontrolled hypertension being treated for Atrial Fibrillation.
Objectives:	**Primary Objective** • To assess the feasibility of concomitant cardiac ablation for the treatment of atrial fibrillation and renal denervation ablation using the EnligHTN renal denervation system in achieving freedom from atrial fibrillation in patients with hypertension. Freedom from atrial fibrillation will be assessed based on electrocardiographic data during nine months following a blanking period of three months. **Secondary Objective** The secondary objectives are: <u>Safety</u> <u>Acute:</u> • The assessment of major adverse cardiac events (within 7 days post procedure) • The assessment of peri-procedure events (within 30 days post procedure) <u>Midterm (6 months):</u> • Assessment of renovascular safety as measured by new renal artery stenosis or aneurysm at the site of ablation • Renal function change based on eGFR (renal denervation group only) • Assessment of major adverse cardiac events <u>Long term (12 months):</u> • Assessment of renovascular safety as measured by new renal artery stenosis or aneurysm at the site of ablation • Renal function change based on eGFR (renal denervation group only) • Assessment of major adverse cardiac events <u>AF Recurrence</u>

	• Recurrence of AF based on electrocardiographic data up to 2 years following the initial cardiac ablation procedure. <u>BP reduction</u> • Percentage of subjects achieving office Systolic Blood Pressure < 140 at 6 months following the initial ablation procedure • Change in Office and Ambulatory Blood Pressure parameters at 6 months following the initial ablation procedure and at the 12 and 24 months visits.

Design:	This is a post market, prospective, multicenter, 2:1 randomized study of the EnligHTN™ Renal Denervation System in conjunction with atrial fibrillation ablation. Up to one hundred subjects with paroxysmal or persistent atrial fibrillation and uncontrolled hypertension will be enrolled in the study. All subjects will undergo cardiac ablation for the treatment of atrial fibrillation. Per the 2:1 randomization, a minimum of 50 or 2/3 of the total patient cohort will also undergo renal artery ablation. Subjects will be followed up to years (2) years post procedure.
	The clinical investigation is anticipated to start in June of 2013. Enrollment is anticipated to end in February of 2014. Subject participation will be up to two (2) years post procedure. Clinical investigation completion in 2016.
Devices used:	EnligHTN™ Renal Artery Ablation Catheter EnligHTN™ RF Generator EnligHTN™ Guiding Catheter (optional) Safire BLU™ Duo or Therapy Cool Path Duo Irrigated Ablation Catheter or Therapy Cool Flex Irrigated Ablation Catheter EnSite Velocity System Agilis NxT Guiding Introducer All devices used in this investigation, have received appropriate certification (and are market released in the geographies participating in this clinical investigation).
Patient Population:	The patient population enrolled in this investigation will consist of male and female patients 18 years of age or older that meet all of the specified inclusion criteria and none of the specified exclusion criteria. These will be patients diagnosed with either persistent or paroxysmal atrial fibrillation and hypertension.
Patient Screening	Patient Screening: Patients that will be treated at the investigational site will be screened by a member of the investigational team. Patients who do not meet the inclusion/exclusion criteria are not eligible to participate. Patients meeting the inclusion/exclusion criteria will be fully informed about the investigation and will be asked to participate in the investigation. A duly signed and dated, Ethics committee (EC) and Sponsor approved, Patient Informed Consent (PIC) will be obtained. A patient becomes a subject once he/she has been fully informed about the investigation, has agreed to participate, signed & dated the Patient Informed Consent (PIC) and therefore has been enrolled in the investigation.
Inclusion Criteria	• Subject is ≥ 18 years of age at time of consent • Subject must be able and willing to provide written informed consent • Subject must be able and willing to comply with the required follow-up schedule • Subject is a candidate for catheter ablation for the treatment of paroxysmal or persistent atrial fibrillation as per the hospital standard of care • Subject has office Systolic Blood Pressure ≥ 140 mmHg at baseline visit • Subject has a daytime mean Systolic Ambulatory Blood Pressure > 135 mmHg within 90 days prior to procedure

	• Subject has established hypertension (diagnosed ≥12 month prior to baseline) and is taking ≥3 anti-hypertensive medications, including 1 diuretic • Subject has been on a stable unchanged anti-hypertensive medication regimen for a minimum of 4 weeks prior to the ablation procedure
Exclusion Criteria	• Subject has long standing atrial fibrillation • Subject has had a previous ablation for atrial fibrillation • Subject has had a previous renal denervation procedure • Subject has had a CABG procedure within the last 180 days (six months) • Subject has a left atrial thrombus • Subject has a contraindication to anticoagulation (i.e. heparin or warfarin) • Subject has unstable angina • Subject has had a myocardial infarction within the previous two months • Subject has a left ventricular ejection fraction (LVEF) <40% as determined by pre-procedure TTE • Subject has significant renovascular abnormalities such as renal artery stenosis > 30% • Subject has undergone prior renal angioplasty, renal denervation, indwelling renal stents, and/or abdominal aortic stent grafts • Subject has hemodynamically significant valvular heart disease as determined by study investigator • Subject has a life expectancy less than 12 months, as determined by the study investigator • Subject is participating in another clinical study • Subject is pregnant, nursing, or of childbearing potential and is not using adequate contraceptive methods • Subject has active systemic infection • Subject has renal arteries < 4 mm in diameter • Subject has an estimated GFR <45 mL/min per 1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula • Subject had a renal transplant or is awaiting a renal transplant • Subject has blood clotting or bleeding abnormalities • Subject has secondary arterial hypertension

Table 1. Study Evaluations

Study Activity	Enrollment / Baseline*	Procedure ≤30 days after Enrollment	Discharge <72 hrs	1M ±7d	3M ±10d	6M ±14d)	12M ±21d	24M ±60d
Consent Process	X							
Inclusion/Exclusion	X							
Medical and Cardiovascular History	X							

Study Activity	**Enrollment / Baseline***	**Procedure ≤30 days after Enrollment**	**Discharge <72 hrs**	**1M** ±7d	**3M ±10d**	**6M** ±14d)	**12M** ±21d	**24M** ±60d
12-Lead ECG	X	X	X	X	X	X	X	X
Office Blood Pressure	X			X	X	X	X	X
Physical Assessment	X			X	X	X	X	X
24-h Ambulatory Blood Pressure	X-performed w/in 90 days prior to procedure					X	X	X
Discharge Blood Pressure			X[b]					
Echocardiography (TTE)	X			X		X	X	X
NYHA Assessment	X			X		X	X	X
Serum creatinine	X					X[t]	X[t]	X[t]
Estimated GFR	X					X[t]	X[t]	X[t]
Hemoglobin A1c	X					X[t]		
Fasting Glucose	X					X[t]		
Fasting Insulin	X					X[t]		
Urine albumin-to-creatinine ratio	X					X[t]		X[t]
Quality of Life Assessment (EQ-5D 5L & AFEQT)	X			X		X	X	X
Renal Artery Anatomy Evaluation	X[t]					X[t]	X[t]	
Pregnancy Test (urine / blood)	X							
Renal Denervation Procedure		X[t]						
Cardiac Ablation Procedure		X						
7 Day Holter or Event Monitor			X		X	X	X	X
Medications	X	X	X	X	X	X	X	X
Adverse Event	**	**	**	**	**	**	**	**
Protocol Deviation	**	**	**	**	**	**	**	**
Withdrawal/ Termination		**	**	**	**	**	**	**

(*) Baseline tests and procedures must be performed within 90 days of Enrollment
(**) as applicable
(b) monitored every 4 hours post procedure until discharge, or for a maximum of 24 hours
(t) only applicable to patients who are in the renal denervation randomization group

2 Background

Hypertension or high blood pressure is a major risk factor for cardiovascular and cerebrovascular events.[1-3] It is responsible for approximately one half of the coronary heart disease and two thirds of the cerebrovascular disease burdens.[4] It is also the world's number one attributable risk for death. The global prevalence of hypertension has been increasing. An analysis indicated that more than one quarter (nearly one billion) of the world's adult population had hypertension in 2000. This is projected to increase to 1.56 billion affected individuals with a prevalence rate of 29% in 2025.[5] This is a major public health challenge in both economically developing and developed countries.

Previous studies showed that drug therapy may reduce the risk of major cardiovascular events by about 20% and the risk of stroke by about 40% in patients with hypertension.[6-10] However, these may not apply to all patients with hypertension. Previous studies of renal denervation have reported varying results. One randomized trial using a different product and conducted in the United States, showed no benefit in blood pressure reduction.[32] Other recent clinical studies reported significant improvement of office blood pressure measurement in patients with resistant hypertension after a catheter-based renal denervation procedure (about -20/-10 mmHg, -25/11 mmHg, -23/-11 mmHg and -32/-14 mmHg at 1, 6, 12 and 24 months respectively from baseline systolic/diastolic blood pressures).[11-14]

Several studies have been published which demonstrate the safety and effectiveness of catheter based renal denervation and its viability as a treatment option for patients with uncontrolled hypertension.[14-16]

Atrial fibrillation (AF) is a common cardiac rhythm disturbance, increasing in prevalence with age. Individuals who develop AF may be at increased risk for stroke, heart failure and death. AF is an extremely expensive public health problem for millions of patients and it has been shown to reduce the quality of life. [17,18] Pharmacological treatment is considered the primary therapeutic option, despite evidence of variable efficacy of antiarrhythmic drug (AAD) therapy, which has a likelihood of AF recurrence (within 6-12 months) of at least 50% for most drugs.[19] Surgical interventions also have their limitations, including the associated risk of death (>1%), permanent pacing (with right side lesions), recurrent bleeding requiring additional surgery, impaired atrial transport functions, and scar-related atrial arrhythmias (atrial flutter). Implantable atrial defibrillators have been shown to treat AF, but the required energy for this purpose is not well tolerated by most patients. Due to the limitations of drug therapy, irrigated catheter ablation systems using Radiofrequency (RF) energy have been developed and have proven effective for long-term arrhythmia control. [17,20-23] However, there is still evidence of AF recurrence even when patients are treated using catheter ablation techniques[17].

It is well known that hypertension is a risk factor for AF, and elevated blood pressure can play a major role in developing and maintaining AF[30,31]. According to the ESC/ESH guidelines for arterial hypertension patients with hypertension and AF are at increased risk for stroke and bleeding complications and should receive strict blood pressure control.[27]

A recent review article evaluated the relationship between renal denervation and its effect on atrial electrophysiology and arrhythmias.[33] Based on the role of the sympathetic nervous system on initiation and perpetuation of atrial fibrillation, the evidence suggests that modulation of autonomic nervous system may be a promising target for intervention in patients with AF.[33] Previous studies have shown the prevention of ventricular and atrial remodeling by renal denervation, suggesting a direct effect of modulating the autonomic nervous system. This regression of left-ventricular hypertrophy has been shown to be associated with a decrease of new-onset AF and may limit the progression of AF. [33]

A recent study evaluated a small cohort of patients (27) with symptomatic AF and drug resistant hypertension. These patients were randomized to either cardiac ablation (pulmonary vein isolation (PVI)) and renal ablation or cardiac ablation (PVI) alone. The renal ablation procedure was completed using a single electrode, irrigated ablation catheter. Their findings demonstrated that 1) renal artery denervation had a positive impact on AF recurrences in hypertensive patients with refractory AF who also underwent PVI; and 2) renal artery ablation resulted in sustained improvement in systolic and diastolic blood pressure control over 1 year of follow-up. Specifically, at the 12-month follow-up examination, 9 (69%) of the 13 PVI with renal artery ablation group patients were AF-free. In contrast, in the PVI-only group, only 4 (29%) of the 14 patients were AF-free on no antiarrhythmic drugs ($p = 0.033$). Additionally, patients who underwent PVI only did not show any significant change in systolic or diastolic blood pressures. By contrast, patients treated with renal denervation displayed a significant decrease in systolic and diastolic blood pressure at each of the visits at 3, 6, 9, and 12 months[25].

3 Investigational Design

3.1 Purpose

The purpose of this post market clinical investigation is to evaluate if concomitant renal denervation with the EnligHTN™ Renal Denervation System and cardiac ablation will result in improved outcomes as compared to ablation alone in patients with uncontrolled hypertension being treated for atrial fibrillation.

3.2 Objectives

Primary Objective

To assess the feasibility of concomitant cardiac ablation for the treatment of atrial fibrillation and renal denervation ablation using the EnligHTN renal denervation system in achieving freedom from atrial fibrillation in patients with hypertension. Freedom from atrial fibrillation will be assessed based on electrocardiographic data during nine months following a blanking period of three months.

Secondary Objective

The secondary objectives are:

<u>Safety</u>

<u>Acute:</u>

- The assessment of major adverse cardiac events (within 7 days post procedure)
- The assessment of peri-procedure events (within 30 days post procedure)

Midterm (6 months):

- Assessment of renovascular safety as measured by new renal artery stenosis or aneurysm at the site of ablation
- Renal function change based on eGFR (renal denervation group only)
- Assessment of major adverse cardiac events

Long term (12 months):

- Assessment of renovascular safety as measured by new renal artery stenosis or aneurysm at the site of ablation
- Renal function change based on eGFR (renal denervation group only)
- Assessment of major adverse cardiac events

AF Recurrence

- Recurrence of AF based on electrocardiographic data up to 2 years following the initial cardiac ablation procedure.

BP reduction

- Percentage of subjects achieving office Systolic Blood Pressure < 140 at 6 month visit
- Change in Office and Ambulatory Blood Pressure parameters at 12 and 24 months following the initial ablation procedure.

3.3 Investigational Type

This is a post market, prospective, multicenter, 2:1 randomized study of the EnligHTN™ Renal Denervation System in conjunction with atrial fibrillation ablation. Up to one hundred subjects with paroxysmal or persistent atrial fibrillation and uncontrolled hypertension will be enrolled in the study. All subjects will undergo cardiac ablation for the treatment of atrial fibrillation. Per the 2:1 randomization, a minimum of 50 or 2/3 of the total patient cohort will also undergo renal artery ablation. Subjects will be followed up to years (2) years post procedure.

3.4 Randomization

Subjects will be randomized in a 2:1 allocation between concomitant cardiac ablation for atrial fibrillation and renal denervation compared to cardiac ablation for atrial fibrillation alone. Randomization will be stratified by each investigational site.

3.5 Patient Population

The patient population enrolled in this investigation will consist of male and female patients 18 years of age or older that meet all of the specified inclusion criteria and none of the specified exclusion criteria (Section 3.7). These will be patients diagnosed with either persistent or paroxysmal atrial fibrillation and hypertension.

According to the ESC consensus statements, based on current evidence from available clinical studies, hypertensive patients are eligible for renal denervation if they have (severe) treatment-resistant hypertension defined by office SBP at least 160 systolic (150mmHg in type 2 diabetes) despite treatment with at least three antihypertensive drugs of different types in adequate doses, including one diuretic, which is equivalent to stage 2 or 3 hypertension[29].

However, in this clinical investigation, the patient population is not only hypertensive, but also suffers from atrial fibrillation. It has been stated in the ESC/ESH guidelines for arterial hypertension that this patient population should be treated differently from patients who suffer from resistant hypertension alone. In these circumstances the guidelines recommend that hypertensive patients with atrial fibrillation require intensive antihypertensive therapy and that additional risks are evident when the SBP exceeds 140mmHg[27]. For this reason, renal denervation should be considered an appropriate and necessary therapy option for atrial fibrillation patients who suffer from hypertension which is drug resistant and exceeds 140mmHg.

3.6 Patient Screening

All patients treated at the investigational site can be screened by a member of the investigational team. This team member needs to be trained on the Clinical Investigational Plan (CIP) and the task of subject screening needs to be delegated in writing to this team member by the Principal Investigator.

The patient will be given ample time to ask questions and to understand the risks of being a part of this investigation. In case the patient agrees to participate, a duly signed and dated Patient Informed Consent (PIC) will be obtained.

3.7 Inclusion and Exclusion Criteria / Point of Enrollment

A patient, who meets all of the inclusion criteria, and none of the exclusion criteria, is eligible to participate in this investigation. A patient becomes a subject once he/she has been fully informed about the investigation, has agreed to participate, signed & dated the PIC and therefore has been enrolled in the investigation. (Refer to section 5.6 for the Informed Consent Process)

Once enrolled, a subject is expected to comply with the scheduled visits and required activities according to the CIP. The subject should undergo the cardiac ablation procedure within 30 days of the baseline visit.

All subjects enrolled in the clinical investigation (including those withdrawn from the clinical investigation or lost to follow-up) shall be accounted for and documented in the Patient Identification Log, assigning an identification code linked to their names, alternative identification

or contact information. Because subject privacy and confidentiality of data must be maintained throughout the clinical investigation, this log will only remain on site.

This log shall be kept up to date throughout the clinical investigation by the Principal Investigator or his/her authorized designee.

3.7.1 Inclusion Criteria

- Subject is ≥ 18 years of age at time of consent
- Subject must be able and willing to provide written informed consent
- Subject must be able and willing to comply with the required follow-up schedule
- Subject is a candidate for catheter ablation for the treatment of paroxysmal or persistent atrial fibrillation as per the hospital standard of care
- Subject has office Systolic Blood Pressure ≥ 140 mmHg at baseline visit
- Subject has a daytime mean Systolic Ambulatory Blood Pressure > 135 mmHg within 90 days prior to procedure
- Subject has established hypertension (diagnosed ≥12 month prior to baseline) and is taking ≥3 anti-hypertensive medications, including 1 diuretic.
- Subject has been on a stable unchanged anti-hypertensive medication regimen for a minimum of 4 weeks prior to the ablation procedure

3.7.2 Exclusion Criteria

- Subject has long standing atrial fibrillation
- Subject has had a previous ablation for atrial fibrillation
- Subject has had a previous renal denervation procedure
- Subject has had a CABG procedure within the last 180 days (six months)
- Subject has a left atrial thrombus
- Subject has a contraindication to anticoagulation (i.e. heparin or warfarin)
- Subject has unstable angina
- Subject has had a myocardial infarction within the previous two months
- Subject has a left ventricular ejection fraction (LVEF) <40% as determined by pre-procedure TTE
- Subject has significant renovascular abnormalities such as renal artery stenosis > 30%
- Subject has undergone prior renal angioplasty, renal denervation, indwelling renal stents, and/or abdominal aortic stent grafts
- Subject has hemodynamically significant valvular heart disease as determined by study investigator
- Subject has a life expectancy less than 12 months, as determined by the study investigator
- Subject is participating in another clinical study
- Subject is pregnant, nursing, or of childbearing potential and is not using adequate contraceptive methods
- Subject has active systemic infection

- Subject has renal arteries < 4 mm in diameter
- Subject has an estimated GFR <45 mL/min per 1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula
- Subject had a renal transplant or is awaiting a renal transplant
- Subject has blood clotting or bleeding abnormalities
- Subject has secondary arterial hypertension

3.8 Procedural Exclusions

Procedurally excluded populations will include subjects who have enrolled in the study and start the procedure, but do not undergo a cardiac ablation procedure for the treatment of atrial fibrillation or if in the renal denervation arm of the study and do not have the EnligHTN™ Renal Denervation System enter his/her body, due to their anatomy, circumstances related to the procedure, or physician judgment. The reason for the procedural exclusion will be documented on the Termination CRF.

3.9 Expected duration of the Investigation

The expected duration of the investigation from first enrollment until final follow-up is approximately three (3) years.

3.10 Expected duration of each subject's participation

The expected duration of each subject enrolled in the clinical investigation is two (2) years.

3.11 Number of subjects required to be included in the Investigation

Using a 2:1 randomization, a total of up to 100 patients will be enrolled in the investigation and will undergo the cardiac ablation procedure. Enough subjects will be enrolled to have at least 50 subjects undergo the concomitant atrial fibrillation ablation and renal denervation procedure in the investigation. Procedurally excluded subjects will not count towards the expected number of treated subjects.

3.12 Estimated time needed to select this subject population

The estimated time needed to enroll the required number of subjects is approximately 8 months.

3.13 Devices Used

3.13.1 Atrial Fibrillation Ablation Procedure

The market approved St. Jude Medical devices to be used in this investigation include:

Safire BLU™ Duo or Therapy Cool Path Duo Irrigated Ablation Catheter or Therapy Cool Flex Irrigated Ablation Catheter
EnSite Velocity System
Agilis NxT Guiding Introducer

3.13.1.1 Atrial Fibrillation Ablation Catheter

Either the Safire BLU™ Duo ablation catheter, the Therapy™ Cool Path™ Duo ablation catheter or the Therapy™ Cool Flex™ ablation catheter will be used to perform the atrial ablation procedure. These catheters are sterile, single use 7F catheters that are constructed of thermoplastic elastomer material and four noble metal electrodes. These catheters have a through-lumen connected to open conduits at the 4mm tip electrode for heparinized saline irrigation during the ablation procedure. The tip curvature may be manipulated by the control mechanism located in the handle at the proximal end of the catheter.

3.13.1.2 3D Mapping System

A 3D electroanatomical mapping system will be used per the center's standard workflow to support the atrial ablation procedure. In particular, the EnSite Velocity**™** Cardiac Mapping System may be used. This is a catheter navigation and mapping system capable of displaying the three dimensional (3D) position of conventional electrophysiology catheters, as well as displaying cardiac electrical activity as waveform traces and as dynamic 3-D isopotential maps of the cardiac chamber. The contoured surfaces of these three-dimensional maps are based on the anatomy of the patient's own cardiac chamber.

3.13.1.3 Guiding Introducer

An Agilis NxT Steerable Introducer will be used to support the left atrial ablation procedure. It is anticipated that it will be used to help guide and maneuver the irrigated ablation catheter as per the center's standard of care. The Agilis NxT is indicated for introducing various cardiovascular catheters into the heart, including the left side of the heart through the interatrial septum

3.13.2 Renal Denervation Procedure

The EnligHTN™ Renal Denervation System is designed to deliver radiofrequency (RF) energy to the renal nerves to achieve targeted denervation. The system consists of the EnligHTN™ RF Ablation Generator (generator), the EnligHTN™ Renal Artery Ablation Catheter (ablation catheter), and the EnligHTN™ Guiding Catheter (optional).

The market approved St. Jude Medical devices to be used in this investigation include:

EnligHTN™ Renal Artery Ablation Catheter
EnligHTN™ RF Generator
EnligHTN™ Guiding Catheter (optional)

3.13.2.1 EnligHTN™ Renal Artery Ablation Catheter

The EnligHTN™ Renal Artery Ablation Catheter is a single use device that has an expandable electrode basket with four Platinum-Iridium (Pt-Ir) ablation electrodes. The electrodes deliver low-level radiofrequency energy to the renal arteries through a percutaneous vascular access site. The distal segment of the ablation catheter is deflectable to assist in proper basket positioning. The handle is used to actuate the expansion and relaxation of the basket, and to

actuate the deflection of the ablation catheter at the distal end. The ablation electrodes and the tip are radiopaque to provide visualization under fluoroscopy.

3.13.2.2 EnligHTN™ RF Ablation Generator

The EnligHTN™ RF Ablation Generator delivers RF energy to the EnligHTN Renal Artery Ablation Catheter using a proprietary algorithm developed to produce a consistent, transmural ablation pattern during the renal denervation procedure.

3.13.2.3 EnligHTN™ Guiding Catheter (optional)

The EnligHTN™ Guiding Catheter system is comprised of two (2) components: a guiding catheter and a dilator. The guiding catheter is constructed of three (3) components: a polytetrafluoroethylene (PTFE) liner, a stainless steel braid, and a multi durometer polymer jacket. The proximal end of the catheter terminates in a hemostasis hub and a hemostasis valve. An extension tube and 3-way stopcock valve is attached to the sideport of the hemostasis hub. The distal end of the catheter terminates in a renal curve with a radiopaque marker embedded in the polymer jacket approximately 2 mm from the catheter tip. The dilator is a polymer tube with an inside diameter sized for guidewire clearance. The proximal end terminates in a snap fitting to mate with the guiding catheter hemostasis hub. The distal end is tapered to facilitate insertion through an introducer sheath.

3.14 Intended Use

The cardiac ablation catheter is indicated for diagnostic and therapeutic use. It has the ability to record intracardiac electrograms and can be utilized for cardiac stimulation during diagnostic electrophysiologic studies/evaluation, as well as for the delivery of RF energy for the treatment of arrhythmias.

The renal denervation ablation catheter is indicated for use in renal denervation procedures for the treatment of hypertension.

4 Procedures

Table 2: Data/CRF Collection

Study Activity	Enrollment / Baseline*	Procedure ≤30 days after Enrollment	Discharge <72 hrs	1M ±7d	3M ±10d	6M ±14d)	12M ±21d	24M ±60d
Consent Process	X							
Inclusion/Exclusion	X							
Medical and Cardiovascular History	X							
12-Lead ECG	X	X	X	X	X	X	X	X
Office Blood Pressure	X			X	X	X	X	X
Physical Assessment	X			X	X	X	X	X
24-h Ambulatory Blood Pressure	X-performed w/in 90 days prior to procedure					X	X	X
Discharge Blood Pressure			X[b]					
Echocardiography (TTE)	X			X		X	X	X
NYHA Assessment	X			X		X	X	X
Serum creatinine	X					X[t]	X[t]	X[t]
Estimated GFR	X					X[t]	X[t]	X[t]
Hemoglobin A1c	X					X[t]		
Fasting Glucose	X					X[t]		
Fasting Insulin	X					X[t]		
Urine albumin-to-creatinine ratio	X					X[t]		X[t]
Quality of Life Assessment (EQ-5D 5L & AFEQT)	X			X		X	X	X
Renal Artery Anatomy Evaluation	X					X[t]	X[t]	
Pregnancy Test (urine / blood)	X							
Renal Denervation Procedure		X[t]						
Cardiac Ablation Procedure		X						

7 Day Holter or Event Monitor			X		X	X	X	X
Medications	X	X	X	X	X	X	X	X
Adverse Event	**	**	**	**	**	**	**	**
CIP Deviation	**	**	**	**	**	**	**	**
Withdrawal/ Termination		**	**	**	**	**	**	**

(*) Baseline tests and procedures must be performed within 90 days of Enrollment.
(**) as applicable
(b) monitored every 4 hours post procedure until discharge, or for a maximum of 24 hours
(t) only applicable to patients who are in the renal denervation randomization group

4.1 Enrollment/Baseline Visit

Prior to enrollment in the clinical investigation, site personnel will screen potential candidates by reviewing the patient medical records against the inclusion and exclusion criteria. It is expected that the medical records will contain adequate and accurate information to determine if the patient meets these criteria. A Screening CRF will be completed for every patient who signs a consent form.

If a patient meets all inclusion criteria and does not meet any of the exclusion criteria, the patient shall be eligible for the investigation.

The study site personnel will follow the informed consent process set forth in Section 5.6. If the patient agrees to participate, the site will obtain the signature and date from the patient on the approved Patient Informed Consent (PIC) form (previously approved by Ethics Committee and the Sponsor). If the patient does not sign and date the Patient Informed Consent (PIC), they cannot participate in the investigation and no further CIP required activities are allowed.

A patient becomes a subject once he/she has been fully informed about the investigation, has agreed to participate, signs and dates the PIC and therefore is enrolled in the investigation.

NOTE: As soon as the subject signs the Patient Informed Consent, adverse events need to be reported according to the guidelines mentioned in Section 5.6.

The EC should be notified appropriately about any CIP deviations with regards to obtaining informed consent.

If new information becomes available during the clinical study that can significantly affect a patient's future health and medical care, that information will be provided to the patient(s) in written form.

The following information will be collected at the baseline visit either from hospital records or through patient interaction documented in the hospital records. All baseline activities will be performed after the patient is enrolled in the investigation. Tests and procedures required at baseline will be completed within 90 days after enrollment and must be completed prior to

procedure. The ablation procedure must be performed within 30 days of the baseline tests and procedures.

4.1.1 Medical History

A complete medical history of the subject will be reviewed and recorded including:

- Hypertension, renal disease, cardiovascular disease, neurological disease, obstructive sleep apnea, hyperlipidemia, diabetes (Type I and II), smoking, thyroid disease, liver disease, chronic obstructive pulmonary disease, and alcohol consumption
- A description of the subject's anti-hypertensive and anti-arrhythmic drug regimen.
- A description of the subject's arrhythmia history.

4.1.2 12-Lead ECG

The subject will undergo a 12-Lead ECG assessment.

4.1.3 Physical Assessment

The subject will have a physical assessment recording at the baseline visit to capture the following:

- Age
- Gender
- Height (only at baseline)
- Weight

4.1.4 Office Blood Pressure

Office Blood Pressure measurements will be recorded as the average Blood Pressure of three measurements. If there is a change in medication after the office Blood Pressure assessment is completed an additional set of office Blood Pressure measurements is required to determine eligibility.

Measurements should be taken according to Standard Joint National Committee VII Guidelines / ESC and ESH Guidelines[26,27], refer to Appendix A for Office Blood Pressure instructions.

4.1.5 Ambulatory Blood Pressure

To ensure proper patient selection for inclusion in the study subjects must have a daytime mean Ambulatory Blood Pressure (ABP) measurement of > 135 mmHg within 90 days prior to procedure.

If there is a change in medication after ABP assessment an additional ABP assessment is required to determine eligibility. In addition to the daytime mean ABP, the night time mean, and 24 hour average ABP value will be collected. When using ABP ensure that at least two measurements per hour are taken during the person's usual waking hours (for example, between 08:00 and 22:00) and 1 measurement per hour are taken during the person's usual night time hours. The average value of at least 14 measurements taken during the person's usual waking hours should be used for calculation of mean daytime value.

Measurements should be taken according to Standard Joint National Committee VII Guidelines ESC and ESH Guidelines[26,27] refer to Appendix B for 24 Hour Ambulatory Blood Pressure instructions.

4.1.6 Blood and Urine Analysis

Blood and urine samples will be collected and analyzed as listed below.

- Serum Creatinine
- Estimated GFR (eGFR)
- Hemoglobin A1c
- Fasting glucose
- Fasting insulin
- Urine albumin-creatinine ratio
- Pregnancy test (only at baseline)

A true numeric value for the estimated GFR must be provided. If your local laboratory does not report the eGFR value beyond 60 mL/min/1.73 m^2 the center should use a sponsor-approved calculation tool to generate the value. The sponsor will provide an approved website(s) for this calculation to study centers.

4.1.7 Transthoracic-echocardiogram (TTE)

Transthoracic-echocardiogram (TTE) examinations will be conducted. Each site is responsible for performing the echocardiogram per their standard of care echo protocol.

4.1.8 NYHA Assessment

NYHA Assessment[28] will be evaluated at baseline and should be classified based on the definitions in Appendix C.

4.1.9 Quality of Life Questionnaire

EQ-5D 5L and the AFEQT questionnaires will be completed at baseline.

4.1.10 Baseline Renal Artery Anatomy Evaluation

Adequate renal artery imaging is required to occur within 90 days prior to enrollment. Computed Tomography (CT) or Magnetic Resonance (MR) angiogram are recommended, non-contrast Magnetic Resonance Imaging (MRI) and doppler evaluation or ultrasound are acceptable. It is recommended that an MRI is performed to evaluate the renal artery anatomy to reduce the risk of radiation exposure.

Renal artery evaluation data collected will include but are not limited to:

- Type of evaluation - computed axial tomography (CT scan), duplex ultrasonography, angiography, Doppler, magnetic resonance (MR) angiography, or non-contrast MRI
- Length of artery(s)
- Diameter of artery(s)
- Number of main renal arteries
- Number of accessory renal arteries
- Presence and percent of stenosis
- Other abnormalities

4.1.11 Medication

The subject's baseline medication regimen, including medication name, dose, and frequency will be reviewed and recorded, making note of those medications taken specific to the subject's cardiovascular therapy. If there is a change in medication after the baseline office Blood Pressure assessment is completed, the patient should be on the new regimen for 4 weeks after which time an additional set of office Blood Pressure measurements is required to determine eligibility.

The investigator will assess that the subject was on a stable anti-hypertensive medication regimen for a period of at least 4 weeks prior to renal denervation procedure. It is recommended that the subjects maintain their enrollment anti-hypertensive regimen for a minimum of 180 days post procedure unless deemed clinically necessary. Investigators will urge subject compliance to prescribed medical regimen throughout the trial. If the subject is non-compliant without medical rationale, the subject may be discontinued from the study.

4.1.12 Adverse Events

Report any adverse events or adverse device effects since consent and document in source documents. Report the adverse event according to specifications in Section 5.7.

4.2 Pre-Cardiac Ablation Procedure

Patients shall undergo pre-ablation tests as per the hospital standard of care to ensure

they can suitably undergo RF catheter ablation therapy for the treatment of paroxysmal or persistent atrial fibrillation.

4.3 Randomization Procedure

Using a 2:1 randomization scheme, each subject will be randomized to an atrial ablation procedure with concomitant renal denervation or an atrial ablation procedure alone.

Each subject will be randomized after the following is completed:
- Baseline evaluation
- Inclusion/Exclusion evaluation
- Subject signs study-specific consent form
- Cardiac ablation procedure for treatment of atrial fibrillation is complete.

4.4 Cardiac Ablation Procedure

Patients will undergo atrial ablation with the Safire Blu Duo, Therapy™ Cool Path Duo or Therapy Cool Flex Ablation Catheter in conjunction a steerable introducer (Agilis NxT) and with the use of the EnSite Velocity System. Any additional navigation and visualization tools or diagnostic catheters may be used at the discretion of the catheter operator and per the center's standard of care.

The ablation strategy utilized for treatment of paroxysmal or persistent atrial fibrillation will follow the center's standard of care and will be recorded on the Procedure Case Report Form.

All cardiac related adverse events occurring during the cardiac ablation procedure will be collected.

4.4.1 Concomitant Cardiac Procedures

Creation of cavo-tricuspid isthmus lesion set for the creation of bi-directional block will be allowed, if the subject has a documented history of typical AFL or if typical AFL is induced during the procedure.

4.4.2 End of Cardiac Ablation

Pacing techniques may be used for determination of electrical isolation of targeted pulmonary veins, bi-directional block along cavo-triscuspid isthmus etc. as applicable. Electrograms (EGM) will be recorded in the source documentation as representation of the techniques used and to ascertain this determination.

The total RF duration, cardiac ablation duration and fluoroscopy times and dosage will be recorded.

4.5 Renal Denervation Procedure

For patients randomized to receive the renal denervation procedure, the procedure should be completed per the institution's standard of care and the study device Instructions for Use.

Procedural data collected will include but is not limited to:

- EnligHTN™ Renal Denervation System device information
- Guiding catheter used – manufacturer
- Number of arteries ablated
- Number of ablations performed
- Device settings
- Procedure time
- Ablation time
- Fluoroscopic time
- Volume of contrast media

4.6 Blanking Period

For three months following the ablation procedure, the subject is in a blanking period while the cardiac tissue recovers from the RF energy application. The AF recurrences during the blanking period will not be reported. If recurrence occurs after the blanking period, the subject will be considered a 'recurrence' according to the primary efficacy endpoint.

4.7 Recurrence of AF

Recurrence is defined as documented atrial fibrillation episode lasting ≥ 30 seconds. An episode of only atrial flutter or an atrial tachycardia will be considered an episode of AF for purposes of recurrence (episodes must be documented and be ≥ 30 seconds in duration). Episodes on 12-lead ECGs are an exception and do not require a ≥ 30 second recording period to be considered a recurrence.

4.8 Re-treatment of AF

Subjects experiencing recurrent atrial arrhythmias may be treated with up to two repeat ablation procedures during the course of the 24 month study. This includes ablation of cardiac arrhythmias that may be responsible for initiating or maintaining atrial fibrillation. The subject's follow-up window will not be re-set, but there will be a 3 month blanking period following the re-treatment procedure.

Re-treatment procedures will follow the ablation procedure as outlined previously in section 4.4, but additional information regarding the completeness of the initial ablation lesions will be recorded. Specifically, entrance and exit block from the pulmonary veins and completeness of any additional lesions lines that were placed will be recorded prior to any new RF energy being delivered. Pre-procedure requirements are at the discretion of the Investigator.

Repeat ablation procedures will count towards the recurrence but will not reset the follow up period. Such patients will continue to be a part of the study and adverse event data will be collected on them throughout their participation in the study.

4.9 Discharge

Prior to discharge, procedures following the center's standard of care post cardiac ablation will be performed.

For all patients, following the ablation procedure(s), the subject's blood pressure will be monitored every 4 hours post procedure until discharge, or for a maximum of 24 hours. At discharge a physical assessment will be performed and the subject's medication regimen will be reviewed and recorded. The patient will also either be given an event recorder or a 7-day holter upon discharge. Discharge is expected to occur ≤72 hours post procedure.

All new adverse events and adverse device effects since enrollment of the subject into the study will be documented on an Adverse Event CRF. The event shall be documented in source documentation and reported according to specifications in section 5.7.

4.10 Follow-up visits

Subjects will return for follow-up at 1 month (±7 days), 3 months (± 10 days), 6 months (± 14 days) post procedure and annual follow-up visits at 12 (± 21 days) and 24 months post-procedure (± 60 days).

The following will be evaluated / reviewed according to Table 1:

4.10.1 Physical Assessment

The subject will have a physical assessment at every follow up visit to capture weight.

4.10.2 Medications

Medications will be recorded in addition to documenting changes to medications at each follow-up visit.

4.10.3 Office Blood Pressure

Office Blood Pressure measurements will be recorded as the average blood pressure of three measurements at each follow-up visit. Measurements should be taken according to Standard Joint National Committee VII Guidelines / ESC and ESH Guidelines [26,27] (Refer to Appendix A for Office Blood Pressure instructions).

4.10.4 24 hour Ambulatory Blood Pressure

24 hour Ambulatory Blood Pressure measurements should be taken according to Standard Joint National Committee VII Guidelines / ESC and ESH Guidelines [26,27](Refer to Appendix B for 24 Hour Ambulatory Blood Pressure instructions) at 6M, 12M, and 24M follow-up visits.

In addition to the daytime mean ABP, the night time mean, and 24 hour average ABP value will be collected. When using ABP ensure that at least two measurements per hour are taken during the person's usual waking hours (for example, between 08:00 and 22:00) and 1 measurement per hour is taken during the person's usual night time hours. The average value of at least 14 measurements taken during the person's usual waking hours should be used for calculation of mean daytime value.

4.10.5 Blood and Urine Analysis

Blood and urine samples will be collected and analyzed as listed below for the renal denervation study cohort

- Serum Creatinine – to be collected at 6M, 12M, and 24M follow-up visit.
- Estimated GFR (eGFR) – to be collected at 6M, 12M, and 24M, follow-up visit.
- Hemoglobin A1c – to be collected at the 6M follow-up visit only
- Fasting glucose – to be collected at the 6M follow-up visit only
- Fasting insulin – to be collected at the 6M follow-up visit only
- Urine albumin to creatinine ratio – to be collected at the 6M, and 24M follow-up visit.

A true numeric value for the estimated GFR must be provided. If your site's laboratory does not report the eGFR value beyond 60 mL/min/1.73 m^2 the center should use a sponsor-approved calculation tool to generate the value. The sponsor will provide an approved website(s) for this calculation to study centers.

4.10.6 Echocardiogram (TTE)

Transthoracic-echocardiogram (TTE) examinations will be conducted at the 1M, 6M, 12M and 24M, follow-up visits. Each site is responsible for performing the echocardiogram per each institutions standard of care echo protocol.

4.10.7 NYHA Assessment

NYHA Assessment[57] will be evaluated at the 1M, 6M, 12M and 24M follow-up visit and should be classified based on the definitions in Appendix C.

4.10.8 EQ-5D 5L Quality of Life Questionnaire

EQ-5D 5L and AFEQT questionnaires will be completed at 1M, 6M, 12M and 24M follow-up visit.

4.10.9 Renal artery evaluation

The renal artery evaluation will only be done in subjects who underwent the renal denervation ablation procedure.

Renal artery evaluation will be completed at the 6M and 12M follow-up visits. This evaluation can be completed by either: computed axial tomography (CT scan), duplex ultrasonography, Doppler, angiography, magnetic resonance (MR) angiography or non contrast magnetic resonance imaging.

If a renal artery evaluation is completed at any other time point during the study, this data will also be collected in the Renal Artery Evaluation CRF.

4.10.10 Assessment of AF Recurrence

Assessment of AF Recurrence will be completed at the 3M, 6M, 12M and 24M follow-up visits viaevaluation of 12 lead ECG recordings, holter monitoring and/or event recorder results. Subjects will be provided 7-day holter monitors for each of these visits or implanted with an event recorder which will be evaluated for the specific 7 day period coinciding with a visit. AF recurrence will not be counted within a 3 month blanking period following the cardiac ablation procedure.

AF Recurrence is defined as episodes lasting longer than 30 seconds in duration. To count as a study-related recurrence, the AF episode must be documented. For this study, AF also includes (documented $\geq$30 seconds) atrial flutter and atrial tachycardia.

4.10.11 Adverse Events

Report any adverse events and adverse device effects since the last visit and document in source documents. Report the adverse event according to specifications in section 5.7.

4.11 Clinical Investigation Termination

Each subject will be followed for 2 years post ablation procedure or until time of death, loss to follow up, withdrawal or clinical investigation termination. The clinical investigation will be complete after all follow-up visits are performed, all data is received by the Sponsor and the database is locked. The study will be closed when a final report is written on the conclusions and analysis of the data.

Participation in this clinical investigation is voluntary. Subjects are free to withdraw from the clinical investigation at any time without reason. However, subjects should be strongly encouraged to complete the protocol required follow up. Should a subject wish to withdraw prior to completing 60-month follow-up, the investigator should request the subject to come in for a final visit and a Termination CRF should be completed by the site and provided to the Sponsor.

At this visit the subject should undergo the following evaluations:

- Office Blood Pressure measurement

- Blood/Urine labs
- 12 Lead ECG

In a situation where a clinical investigation withdrawal is due to an adverse event the subject should be followed until resolution of that adverse event or determination that the subject's condition is stable. Upon withdrawal from the study, data will cease to be collected on Case Report Forms.

Subjects must be informed about their right to withdraw from the investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled and withdrawal from the investigation will not jeopardize their future medical care or relationship with the investigator. Subjects will be asked to specify the reason for the withdrawal, but have the right not to answer.

The investigator may decide to withdraw a subject from the investigation at any time. The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the investigation. All reasonable efforts should be made to retain the subject in the clinical investigation until completion of the investigation.

Reasons for termination include, but are not limited to, the following:

- Subject did not meet the inclusion/exclusion criteria
- Subject requests to be withdrawn from the study
- Investigator withdraws subject from the study
- Subject lost to follow-up, defined as the following: a subject will be considered "lost to follow-up" after a minimum of 2 documented phone calls of a physician or delegate at the study site to the subject or emergency contact and a certified letter sent to the last known address
    - Subject death (in case of subject death, cause must be documented)
    - Subject non-compliance
- Study terminated at the local, national, or international level, at the request of Ethics Committees, regulatory authorities, or SJM.
- Subject completed study

4.12 Description of post investigational provision of medical care

When the subject's participation in the clinical investigation has been completed (prematurely) or terminated, the subject will return to the medical care as per physician's recommendation.

5 Clinical Investigation Conduct

5.1 Ethics Committee

A duly constituted EC representing the prospective study site must review and approve the subject informed consent, the clinical investigation plan, the prospective investigator's participation in the study, and any other study related information to be provided to the subjects

prior to subject enrollment. Additionally, the Investigator must be aware of and adhere to all EC requirements such as, but not limited to: the submission of progress reports, serious adverse events, and protocol deviations.

EC approval record should clearly identify:

- the date of the meeting
- constitution of the committee and voting members present at the meeting
- the approved version of the Clinical Investigation Plan
- the approved version of the Patient Information Sheet and Patient Informed Consent
- the approved version of the Instructions for Use (IFU)

Approval from the EC is necessary prior to the start of the investigation. The original approval is to be filed in the Investigator Study Binder and a copy of the approval is provided to SJM prior to commencing study activities.

Any amendments to the protocol should be submitted to the relevant EC. The EC will be informed about SAEs and UADEs in accordance with local and national requirements.

5.2 Ethical Basis

This clinical investigation will be performed in accordance with the World Medical Association Declaration of Helsinki (Appendix F) and applicable local and national legal and regulatory requirements. Prior to starting the investigation, the Clinical Investigation Plan will be submitted together with associated documents including Patient Information Sheets, and subject Informed Consent Forms in the local language to the relevant EC for review.

5.3 Insurance

St. Jude Medical, as the Sponsor, has taken out insurance for all subjects participating in this study in accordance with the requirements of the local laws.

5.4 Statements of Compliance

The investigation will be performed in accordance with the most current versions of the World Medical Association (WMA) Declaration of Helsinki and any regional and/or national regulations, as appropriate.

The investigator shall not start enrolling subjects or requesting informed consent prior to obtaining Ethics Committee approval and authorization from the sponsor in writing for the investigation.

In case additional requirements are imposed by the Ethics Committee, they shall be followed, if appropriate.

As sponsor, SJM will maintain insurance for this investigation in accordance with the requirements of the applicable local laws.

5.5 Adherence to the Clinical Investigation Plan

The Principal Investigator and delegates are required to adhere to the CIP in order to prevent subjects being exposed to unreasonable risks. The Principal Investigator and delegates are also required to be compliant with the signed Study Agreement, applicable national or local laws and regulations, and any conditions required by the appropriate EC or applicable regulatory authorities. Instances of failure, intentionally or unintentionally, to adhere to the requirements of the CIP are considered a deviation and corrective action(s) may be taken to prevent these instances from occurring again.

In some cases failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of subjects, since the non-compliance potentially exposes subjects to unreasonable risks. For example, failure to adhere to the inclusion/exclusion criteria: these criteria are specifically defined by the Sponsor to exclude subjects for whom the device is not beneficial and the use involves unreasonable risks. This may be considered failure to protect the rights, safety and well-being of the enrolled subject. Similarly, failure to perform safety assessments intended to detect adverse events may be considered failure to protect the rights, safety and well-being of the enrolled subject. Investigators should minimize such risks by adhering to the CIP.

Simultaneously, in the event that adhering to the CIP might expose the subject to unreasonable risks, the investigator is also required to protect the rights, safety and well-being of the subject by intentionally deviating from the requirements of the CIP, so that subjects are not exposed to unreasonable risks. It is the responsibility of the investigator to provide adequate medical care to a subject enrolled in an investigation.

The PI shall promptly report any deviations from the CIP to the Sponsor that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances. The reporting of these deviations should be done as soon as possible but no later than 72 hours after the investigator becomes aware. The investigator shall also promptly notify the EC per their requirements.

Any corrective and preventive actions required by the EC must be complied with by the site.

The Sponsor will notify the EC as per their requirements.

5.5.1 Repeated non-compliance

In the event of repeated non-compliance, as determined by the Sponsor, a Clinical Research Associate or sponsor representative will attempt to secure compliance by one or more of the following actions:

- Visiting the investigator
- Contacting the investigator by telephone
- Contacting the investigator in writing
- Retraining of the investigator

If an investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical investigation, the Sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical investigation.

5.6 Informed Consent Process

5.6.1 General Process

Provision of the Informed Consent is mandatory. Informed Consent is required from all patients prior to participation in the investigation. The process of obtaining Informed Consent shall comply with the most recent version of the Declaration of Helsinki, ISO 14155:2011 and all applicable regulations.

The Principal Investigator or his/her authorized designee will conduct the Informed Consent Process. This process will include a verbal discussion with the patient on all aspects of the clinical investigation that are relevant to the patient's decision to participate in the clinical investigation. It is crucial that this discussion is documented in the source documents (hospital records).

Prior to enrolling in the clinical study, patients shall be fully informed of the details of clinical study participation as required by applicable regulations and the study center's EC, and/or Head of Medical Institution. Informed consent must be obtained from each patient prior to any clinical study participation using the Patient Information Sheet (PIS) and Patient Informed Consent form (PIC) approved by both the Sponsor, and the study center's EC,. Prior to the patient signing the PIS, the investigator or authorized delegate will fully explain to the patient the nature of the research, clinical study procedures, anticipated benefits, and potential risks of participation in the clinical study.

The patient will be provided with the EC approved patient information sheet and informed consent form that is written in a language that is understandable to them (native non technical language) and sufficient time is provided to the patient to consider participation and ask questions if necessary. The study site personnel will provide answers to the patient's questions.

If a patient is unable to read or write, the consenting shall be obtained through a supervised oral process. An independent witness shall be present throughout the process. The consent form must be signed and dated by the patient and by the person obtaining the consent attesting that the information was accurately explained and that informed consent was freely given.

If the patient does not sign and date the PIC, he/she cannot participate in the investigation, and no further CIP required activities are allowed. If the patient has provided written informed consent, signature and date from the Principal Investigator or authorized designee will be obtained on the EC approved informed consent form.
In order to avoid any possible coercion or undue improper influence on, or inducement of the patient to participate, the Sponsor requests the investigator to only sign the informed consent form once the subject has signed and dated the document and therefore decided to participate in the investigation.

Informed Consent of a subject shall always be indicated by personally dated signature of the subject and by the investigator responsible for conducting the Informed Consent process.

The original signed consent document must be retained on file by the investigator and a copy of the signed consent document is provided to the subject (investigator's responsibility).

The subject's legal rights will not be waived, nor will it appear that these will be waived.

Important new information that becomes available throughout the clinical investigation will have to be provided in writing to new and existing subjects. If relevant, all affected subjects will be provided a new consent form to review and re-sign, should they decide to maintain participation in the investigation.

5.7 Adverse Event, Adverse Device Effect

Definitions

The definitions provided below are in accordance to ISO 14155:2011 (E).

5.7.1 Medical device

Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article.

- Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of
    - Diagnosis, prevention, monitoring, treatments or alleviation of disease,
    - Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
    - Investigation, replacement, modification, or support of the anatomy or of a physiological process,
    - Supporting or sustaining life,
    - Control of conception,
    - Disinfection of medical devices and
- Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

5.7.2 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device.

Note: This definition includes events related to the medical device or the comparator.
Note: This definition includes events related to the procedures involved.

5.7.3 Serious Adverse Event (SAE)

An adverse event that led to:

- Death

- A serious deterioration in the health of the subject, that either resulted in:
  - A life-threatening illness or injury OR
  - A permanent impairment to a body structure or a body function OR
  - An in-patient or prolonged hospitalization OR
  - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body OR
  - A malignant tumor
- Fetal distress, fetal death or a congenital abnormality or birth defect

Note: A 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.

5.7.4 Adverse Device Effect (ADE)

An adverse event related to the use of an investigational device.

Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device.

Note: This definition includes any event resulting from the use error or from intentional misuse of the medical device.

5.7.5 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

5.7.6 Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

5.7.7 Anticipated Serious Adverse Device Effect (ASADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

5.7.8 Procedure for assessing, recording and reporting adverse events, adverse device effects, serious adverse events and serious adverse device effects*:*

Safety surveillance and reporting will be done for all subjects enrolled in this investigation as described below.

Safety surveillance within this investigation and the safety reporting performed by the investigator, starts as soon as the subject is enrolled in this investigation (date of signature of the informed consent). The safety surveillance and the safety reporting will continue until the last

investigational visit has been performed or the subject is deceased or the subject/investigator concludes his participation into the investigation.

For the purpose of this trial, all Serious Adverse Events and all Adverse Device Effects (regardless of severity) are to be documented and reported to the sponsor immediately and this no later than 72 hours after becoming aware of the event.
Adverse events will be assessed by the investigator for relationship to the device and to the procedures involved.

- Procedure related: The AE is deemed related to the procedure if it occurred during the procedure but was not directly caused by the medical device.
- Device related: The AE is deemed device related if it was directly caused by the medical device.

Investigators are responsible for promptly reporting all SAEs and ADEs to the sponsor by completing the Adverse Event form. All unresolved AEs should be followed by the investigator until resolution is reached.

Note: Refer to Table 1 'Data Collection' and Appendix G 'Data Collection Method'.
In case of EDC failure, notify Sponsor via Fax (+800 2546 2546) or via *AdverseEvent@sjm.com.*

5.8 Subject Death

5.8.1 Procedure for recording and reporting Subject Death

The investigator will document and report all subject deaths to the sponsor immediately but no later than 72 hours after becoming aware of the event.

Should death occur, the investigator should record the information in the hospital records and immediately document the information on the Death Form. By completing the form the sponsor will be notified.

Note: Refer to Table 1 'Data Collection' and Appendix G 'Data Collection Method'
In case of EDC failure, notify Sponsor via Fax (+800 2546 2546) or via *AdverseEvent@sjm.com.*

Subject Death can be an outcome of a serious adverse event (SAE). Death can therefore be related to an SAE and all efforts to obtain the SAE details should be made and the Adverse Event form must be completed. Any supporting documentation (autopsy records, death certificates, hospitalization records) must be sent to SJM with the corresponding SAE and Death CRFs.

The subject's death is an Early Conclusion of the subject's participation in the investigation. Therefore, the investigator is requested to complete the Termination form.

The investigator must notify the EC, if appropriate, in accordance with national and local laws and regulations.

5.9 Document and data control

5.9.1 Traceability of documents and data

The investigator shall ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the electronic case report forms (eCRFs) and in all required reports. When copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigational site team with a statement that it is a true reproduction of the original source document.

5.9.2 Recording data

Source documents shall be created and maintained by the investigational site team throughout the clinical investigation.

The data reported on the eCRFs shall be derived from, and be consistent with, source documents, and any discrepancies shall be explained in writing.

The eCRFs shall be validated by the Principal Investigator or a delegated investigator. Any change or correction to data reported shall be dated and explained if necessary. The original entry will remain available by audit trail.

5.9.3 Review of data

The clinical investigation will be monitored by reviewing the eCRF approved by the investigators.

The following activities will occur:

- All eCRFs will be reviewed for completeness and accuracy after being uploaded into the database.
- The investigator (co-investigator) and/or delegate is notified regarding any missing or unclear/inconsistent data.

5.10 Monitoring

On site-monitoring shall be performed during the clinical investigation in order to guarantee adherence to all applicable regulations, the Clinical Investigation Plan and the signed Clinical Study Agreement. By monitoring, the Sponsor can also verify the accuracy of data collected on the accompanying eCRFs throughout the duration of the clinical investigation.

Monitoring is necessary to ensure adequate protection of the rights and safety of human subjects involved in the clinical investigation and the quality and integrity of the data obtained during the investigation. The sponsor will at the same time assess the investigational site and study team on staffing and facilities to ensure the investigation can continue in a safe and effective fashion.

During the monitoring visits, data reported on the eCRF shall be reviewed as specified in the monitoring plan.

5.10.1 Designated Monitors

Only monitors qualified by education, training and experience, which have been trained on the Clinical Investigation Plan, eCRF content, Monitoring Plan, relevant requirements and informed consent process will be allowed to perform monitoring activities during this clinical investigation. The monitor's qualifications and training will be documented by the sponsor. A list of monitors is available upon request.

5.10.2 Monitoring Plan

Prior to the start of the site monitoring activities for this clinical investigation, a project specific Monitoring Plan (MP) will be created.

At a minimum, the Monitoring Plan will include the following:

- Required activities
- Frequency of monitoring visits
- Visit Requirements
- Procedures for securing site compliance
- Monitoring report content and timelines
- Close-out procedures

The Monitoring Plan may be updated as appropriate. All revisions will be tracked.

5.11 Competent Authority (CA) Inspections

The investigator and/or delegate should contact SJM immediately upon notification of a CA inspection at the site. A clinical monitor will assist the investigator and/or delegate in preparing for the inspection.

An investigator who has authority to grant access shall permit authorized CA employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are used or where records or results are kept).

An investigator, or any person acting on behalf of such a person with respect to the investigation, shall permit authorized CA employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the investigation.

An investigator shall permit authorized CA employees to inspect and copy records that identify subjects, upon notice that CA 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 EC have not been submitted or are incomplete, inaccurate, false or misleading.

5.12 Investigation Termination

The Sponsor reserves the right to suspend or terminate the investigation in an individual site or the entire clinical investigation for significant and documented reasons, at any stage, with appropriate written notice to the investigator.

The investigation will be terminated according to applicable regulations.

The investigator shall return all documents to the sponsor and notify the Ethics Committee and the Competent Authority (if applicable). Follow-up for all enrolled subjects will be as per standard of care.

5.12.1 Resuming the Clinical Investigation after Suspension

The sponsor shall conclude an analysis of the reason(s) for the suspension, implement the necessary corrective actions, and decide to lift the temporary suspension. The sponsor shall inform the Principal Investigators, EC/Head of Medical Institution or regulatory authority, where appropriate, and the regulatory authority of the rationale, providing them with the relevant data supporting this decision.

Concurrence shall be obtained from the, EC/Head of Medical Institution or regulatory authority where appropriate, before the clinical investigation resumes.

If subjects have been informed of the suspension, the Principal Investigator or authorized designee shall inform them of the reasons for resumption.

5.12.2 Investigation Conclusion

The investigation will be concluded when:

- A Close Out visit has been performed at each participating center AND
- The Final report has been provided by the sponsor

6 Risks and Benefits of the Clinical Investigation

6.1 Anticipated Adverse Events and Adverse Device Effects

Possible adverse events associated with the cardiac ablation procedure include, but are not limited to:

Cardiac Events:

- Abnormal ECG
- Angina (chest pain)
- Arrhythmia
- AV fistula
- Complete heart block
- Coronary artery injury
- Cardiac Perforation
- Cardiac Thromboembolism
- Myocardial infarction
- Obstruction/perforation/damage of the vascular system
- Death
- Dislodgement of implantable cardioverter defibrillator permanent pacing lead
- Endocarditis
- Exacerbation of pre-existing atrial fibrillation
- Heart Failure
- Hypotension
heart block)
- Left atrial / esophageal fistula
- Pulmonary vein dissection
- Pulmonary vein stenosis

- Palpitation
- Pericardial effusion/cardiac tamponade
- Pericardial effusion without tamponade
- Pericarditis
- CHF exacerbation – fluid overload
- Component damage to ICD or implantable pacemaker
- Pulmonary vein thrombus
- Temporary or complete heart block
- Unintended (in)complete AV, sinus node, heart block/damage
- Vessel wall/valvular damage or insufficiency
- Ventricular arrhythmia requiring defibrillation
- Bradycardia

Non-Cardiac Events:

- Air embolism
- Anesthesia reaction
- Cerebrovascular accident
- High creatinine phosphokinase (CPK)
- Infections
- Local hematomas / ecchymosis
- Laceration
- Phrenic nerve damage
- Pneumonia
- Pneumothorax
- Vasospasm
- Pulmonary edema
- Pulmonary embolism
- Pulmonary hypertension
- Pleural effusion
- Pseudoaneurysm
- Respiratory depression
- Skin burns
- Syncope
- Transient ischemic attack
- Vasovagal reactions
- Vasovagal episodes

Possible adverse events associated with the renal denervation procedure include, but are not limited to:

- Acute renal injury (renal infarction, renal hematoma)
- Renal vascular injury (renal artery dissection, renal artery thrombosis, renal artery stenosis)
- Collateral tissue injury
- Malignant or accelerated hypertension
- Symptomatic hypotension
- Access site complications (arteriovenous fistula, access site thrombosis, embolisation, pseudo-aneurysm, hematoma, limb ischemia, femoral nerve injury, or seroma)
- Disseminated intravascular coagulation
- Infection (access site infection or systemic infection)
- Renal failure
- Decompensated heart failure
- Myocardial infarction
- Neurologic event (acute ischemic or hemorrhagic brain injury)
- Respiratory compromise
- Pain, including back pain
- Death
- Drug reactions
- Contrast allergies etc

6.2 Steps that will be taken to control or mitigate the risks

Every possible effort will be taken to minimize the risks, including:

- Careful selection of experienced investigators for the clinical investigation
- Regular clinical investigation monitoring visits for each clinical investigation center
- Conduction of the clinical investigation in accordance with the Clinical Investigational Plan (CIP), all applicable laws and regulations (e.g. ISO14155:2011) and any conditions of approval imposed by the appropriate EC or applicable regulatory authorities where the clinical investigation is performed
- Performance of the cardiac ablation procedure in accordance with device IFUs.
- Preparation of the catheter and performance of the renal denervation procedure in accordance with the device IFUs.
- Catheter advancement under fluoroscopic imaging to minimize the risk of arterial damage.
- Training of Investigators both on the CIP and EnligHTN Renal Denervation procedure

6.3 Potential Benefits

There may not be any benefits from this research. For subjects randomized to the renal denervation arm of the study, possible benefits may include a decrease in blood pressure, which may also have beneficial effects on the heart such as a reduced chance of arrhythmia recurrence. Previous studies of renal denervation have reported varying results. One randomized trial using a different product and conducted in the United States, showed no benefit in blood pressure reduction.[32] The RD+AF trial uses a different product and aims to study the impact of renal denervation on atrial fibrillation. Less than 20% of patients in previous studies had no significant reduction in blood pressure and the majority of patients in a small study had an improvement in the atrial fibrillation recurrence. Information gathered from this study will add to the understanding of the treatment options for patients with atrial fibrillation and high blood pressure. This knowledge may advance medical science and may, in turn, benefit other patients with atrial fibrillation and high blood pressure.

7 Statistical Analysis

7.1 Study design

This is a post market, prospective, multicenter, 2:1 randomized study of the EnligHTN™ Renal Denervation System in conjunction with atrial fibrillation ablation. Up to one hundred subjects with paroxysmal or persistent atrial fibrillation and uncontrolled hypertension will undergo atrial fibrillation ablation. Per the 2:1 randomization, a minimum of 50 or 2/3 of the total patient cohort will also undergo renal artery ablation. Subjects will be followed up to years (2) years post procedure.

To assess the feasibility of concomitant cardiac ablation for the treatment of atrial fibrillation and renal denervation ablation using the EnligHTN renal denervation system in achieving freedom

from atrial fibrillation in patients with hypertension. Freedom from atrial fibrillation will be assessed based on electrocardiographic data during nine months following the blanking period.

7.2 Sample size estimation

The sample size of approximately 100 patients is used considering the study purpose: to complete a preliminary evaluation on whether or not concomitant renal denervation with the EnligHTN™ Renal Denervation System and cardiac ablation will result in improved outcomes as compared to ablation alone in patients being treated for Atrial Fibrillation. Of these patients, a minimum of 50 patients (or 2/3 of the total patient cohort) will undergo both a cardiac ablation procedure and a concomitant renal denervation procedure.

No formal power analysis or hypothesis test will be performed. However the data collected will be analyzed and presented using the descriptive or appropriate summary statistics.

7.3 Analysis Population

All patients who have signed a Patient Informed Consent (PIC) will be considered enrolled in the study. However, the Primary Analysis population will only include those patients that have signed a PIC, have undergone a cardiac ablation procedure for the treatment of atrial fibrillation, and, if in the renal denervation arm of the study, had the EnligHTN™ Renal Denervation System enter his/her body.

It is anticipated that there may be subjects who have been enrolled in the study but are not included in the Primary Analysis population, such as:

- Subjects who are enrolled but do not meet baseline inclusion or exclusion criteria before the procedure; these are considered the screen failure population.
- Procedurally excluded populations will include subjects who have enrolled in the study and start the procedure, but do not undergo a cardiac ablation procedure for the treatment of atrial fibrillation or if in the renal denervation arm of the study and do not have the EnligHTN™ Renal Denervation System enter his/her body, due to their anatomy, circumstances related to the procedure, or physician judgment.

Subjects who withdraw from the investigation will not be replaced in any analysis population.

7.4 Data Analysis and Reporting

Data analysis will be performed across all subjects based on Primary Analysis population unless otherwise specified.

The data collected will be presented using the appropriate summary statistics. Continuous data will be summarized using descriptive statistics (mean, number of observations, standard

deviation, minimum and/or maximum values) and categorical data will be summarized using frequencies and percentages.

7.4.1 Primary objective

The primary objective is to assess the feasibility of concomitant cardiac ablation for the treatment of atrial fibrillation and renal denervation ablation using the EnligHTN renal denervation system in achieving freedom from atrial fibrillation in patients with hypertension.
The freedom from atrial fibrillation will be assessed based on electrocardiographic data during nine months following the blanking period including the one week recording coinciding with the 12 month follow-up visit (9 months following the 3 month blanking period).

Assessment of the AF recurrence will be determined through evaluation of 12 lead ECG recordings, holter monitoring or event recorder results. Subjects will be provided 7-day holter monitors for each of the follow up visits or implanted with an event recorder which will be evaluated for the specific 7 day period coinciding with a visit. AF recurrence will not be counted within a 3 month blanking period following the ablation procedure. AF Recurrence is defined as episodes lasting longer than 30 seconds in duration. To count as a study-related recurrence, the AF episode must be documented. For this study, AF also includes (documented $\geq$30 seconds) atrial flutter and atrial tachycardia.

7.4.2 The Secondary objectives

7.4.2.1 Safety Acute data

The major adverse cardiac events within 7 days post procedure will be summarized as a percentage of patients as defined as:$\frac{Number\ of\ subjects\ with\ \text{major adverse cardiac events within 7 days post procedure}}{Number\ of\ subjects\ at\ baseline\ for\ that\ population} * 100$

- The peri-procedural events within 30 days post procedure will be summarized as a percentage of patients as described above.

7.4.2.2 Safety Midterm (6 months) and Long term (1-2 years) data

For all patients, the major adverse cardiac events will be recorded.

For patients undergoing the renal denervation procedure:

- The new renal artery stenosis (>50%) and/or aneurysm at the site of ablation per Renal Artery Imaging will be summarized at 6 and 12 months as percentage of patients who have stenosis and/or aneurysm. Image interpretation will be based on local analysis. Kaplan-meier analysis may be performed on the time to the first new renal artery stenosis and/or aneurysm at the site of ablation
- Renal function change based on eGFR will be summarized by:

1. Computing the change of the eGFR at 6 months, 12 months and 2 years compared to baseline for each patient with data available in both time points.

2. Calculating the mean and standard deviation of the eGFR change at those intervals

7.4.2.3 AF Recurrence

The primary endpoint will evaluate recurrence of AF during the 9 months following the blanking period. Secondarily, the recurrence of AF based on electrocardiographic data at 3 months, 6 months and 24 months will also be reported.

- Assessment of the AF recurrence will be determined through evaluation of 12 lead ECG recordings, holter monitoring or event recorder results. AF Recurrence is defined as episodes lasting longer than 30 seconds in duration. To count as a study-related recurrence, the AF episode must be documented. For this study, AF recurrence also includes (documented ≥30 seconds) atrial flutter and atrial tachycardia.

7.4.2.4 BP reduction

The mean reduction of office SBP at six (6) months of the study will be analyzed by:

1. Computing the reduction of SBP measurements at 6 months compared to baseline for each patient with data available in both time points.

2. Calculating the mean and standard deviation of the SBP reduction at 6 months

The data of

- Change in Ambulatory Blood Pressure parameters at 6 months,
- Change in Office Diastolic Blood Pressure at 6 months,
- Change in Office and Ambulatory Blood Pressure parameters

at 12 and 24 months post denervation will be calculated in the same way as described in the calculation of SBP reduction at 6 months.

- The percentage of subjects achieving office SBP < 140 at 6 months visit will be computed as follows:

$$\frac{Number\ of\ subjects\ achieving\ office\ SBP\ <\ 140\ at\ 6\ months\ visit}{Number\ of\ subjects\ \ with\ \ data\ available\ in\ 6\ months\ visit} * 100$$

7.4.3 Other Analyses

In addition, subgroup analyses may be performed as needed, e.g.:

- for subjects that have the renal denervation procedure performed on one side but not the other (due to their anatomy, circumstances related to the procedure, or physician judgment)
- based on the number of ablation points performed
- by the subject's primary disease conditions.

Ad hoc analyses may be performed as needed. Analysis may be performed based on As Treated population as appropriated. In general, data analysis will be performed on a per subject basis. But the data analysis may be presented per kidney, or on renal artery basis, as appropriate.

7.4.4 Analysis Software

The statistical analyses will be performed using SAS™ software version 9.2, or as specified and appropriate.

8 Data Management

All documents and data shall be produced and maintained in a way that assures control and traceability. Where relevant, the accuracy of translations shall be guaranteed and documented. All documents, and subsequent versions, related to a clinical investigation shall be identifiable, traceable and appropriately stored to provide a complete history of the clinical investigation.

eCRFs shall be developed by Sponsor to capture the data for each enrolled subject as required by the CIP. The eCRFs shall include information on the condition of each subject upon entering, and during the course of the clinical investigation, exposure to the device and any other therapies.

The Sponsor will be responsible for the data handling.

Data will be analyzed by the Sponsor and may be transferred to the Sponsor's locations worldwide and/or any other worldwide regulatory authorities in support of a market-approval application.

8.1 Data Management Plan

eCRF data will be entered by authorized investigative site personnel in a validated electronic database.

The Data Management Plan (DMP) describes all the computerized data cleaning checks (validation rules) as programmed at the time of database set-up. These validation rules may change and be updated throughout the course of the investigation.

Manual review and Data Cleaning Convention (DCC) will be used in addition to computerized data cleaning checks, to check for discrepancies and to ensure consistency of the data.

All revisions of the DMP will be tracked and include an effective date.

8.2 Source Documents

Source documents shall be maintained by the investigation site team throughout the clinical study. All findings in this clinical study must be documented as source data, and therefore can be verified (and audited). Source documentation may be paper or electronic, and is defined as the first time the data appears and may include for example; all clinical records, hospital records, surgery reports, autopsy reports, and any other material that contains original information used for clinical study data collection or adverse event reporting.

8.3 Source Data and Subject Files

The investigator shall keep written or electronic subject files for every subject participating in the clinical investigation. In this file, which will be kept on site, the available demographic and medical information of a subject shall be documented, in particular the following:

Name	Age	Weight

Gender	Height	Concomitant Medication
Subject History	Concomitant diseases	Scheduled follow ups
PIC process	Date of PIC	Observed AEs
CIP required examination	Clinical findings	Procedure Notes

It should be possible to verify the inclusion and exclusion criteria for the investigation from the available data in this file. It must be possible to identify each subject by using this subject file. Additionally, any other documents with source data have to bear at least the subject identification and the printing date printed by the recording device to indicate to which subject and to which procedure the document belongs. The medical evaluation of such records should be documented as necessary and signed/dated by the investigator. All data recorded on the eCRF must be part of the subject's source data.

8.4 Confidentiality of Data

All subject information collected during the course of this study will be kept strictly confidential according to applicable country-specific laws and regulations. All data and information concerning subjects and their participation in this study are considered confidential by St. Jude Medical, Cardiology Division, Inc., d/b/a St. Jude Medical, Cardiovascular Division, Inc., a U.S. company, and its affiliates (located in the U.S.A. and European Economic Area (EEA), Canada, and other countries), and other people who work for SJM to provide services related to the device and this study (collectively referred to as "SJM"). All public reporting of the results of the study will eliminate identifiable references to the subjects. Information on paper will be kept in secured locations. Electronic information will be kept on password-protected computers.

Personal data, including medical and health information, will be processed both by computer and manually, during and after the study by SJM, and its affiliates, its designated third party data processors, the EC, the institution conducting the study, the study doctors and other healthcare personnel involved in the study for the purposes of this study. The electronic data stored for this study will be kept in an SJM database, in compliance with applicable law. Subject data will not contain details of study subject identity. The data will be stored on a secure server and backed up routinely. Personal data will be key-coded to prevent subject identification, except by the institution, study doctors and other healthcare personnel involved in the study, if necessary for the purpose of the study, for regulatory inspections, and to comply with SJM reporting obligations.

Study subjects have a right to gain access and to correct inaccuracies in information about them as permitted by applicable law.

In order to help keep subject medical records and personal information confidential only certain authorized investigators and SJM personnel, or approved contracted agents of SJM, will have access to confidential records. These include researchers in the hospital who are part of this study, SJM and its affiliates and representatives that perform study-related services who may be located in the U.S.A., Canada, European Economic Area (EEA) and other countries. The Ethics Committee (EC) and other regulatory authorities also have the right to inspect and copy records pertinent to this study. It is necessary for them to review study data, portions of study subject records and information so that they can follow the study progress, which may include without limitation:

- Monitor the accuracy and completeness of the study
- Perform scientific analysis and develop the medical product
- And/or obtain approval to market the medical products in the USA, Canada, EEA, and other countries.

Any information about subjects that leaves the institution conducting the study will be modified to remove certain information that could identify the subject (e.g., subject's name, age on the day of enrollment, address, and hospital number) and only be identifiable by a study specific subject ID code. Study data provided to SJM that is published in medical journals and/or presented at scientific conferences will not allow the identification of study subjects.

The results of the study will be made available to SJM and its affiliates (located in the U.S.A., EEA, Canada, and other countries) and other people who work for SJM to provide services related to the device and this study and study center.

A summary of the information on all subjects may be provided to governmental agencies (including regulatory agencies), regulatory authorities in the U.S.A., Canada, EEA and other countries who may also need to review study data and portions of medical records. Results from this study may also be published in scientific journals or presented at conferences as an oral or poster presentation; however, the identity of a study subject will not be disclosed.

9 Document Retention

The Principal Investigator (PI) shall maintain all essential clinical investigation documents from prior, during and (as specified) after the clinical investigation on file at the site for a minimum of 15 years after the termination of this investigation, or longer as per local laws, or when it is no longer needed to support a marketing application, whichever is later.

The PI must contact the sponsor prior to destroying or archiving off-site any records and reports pertaining to this investigation to ensure that they no longer need to be retained on-site.

All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the sponsor.

All data and documents shall be made available on request of the relevant authorities in case of an audit.

The sponsor will archive and retain all essential clinical investigation documents from prior, during and (as specified) after the clinical investigation as per requirements.

10 Amendments to the Clinical Investigational Plan

The CIP, eCRFs, Patient Informed Consent form and other subject information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Proposed amendments to the CIP shall be agreed upon between the Sponsor and Principal Investigator, or the Coordinating Investigator.

The amendments to the CIP and the Patient Informed Consent shall be notified to, or approved by, the EC and regulatory authorities, if required. The version number and date of amendments shall be documented.

The amendment will identify the changes made, the reason for the changes and if it is mandatory or optional to implement the amendment.

Any amendment affecting the subject requires that the subject be informed of the changes and a new Patient Informed Consent be signed and dated by the investigator and subject prior to the subject's next follow up.

Changes to, or formal clarifications of, the CIP will be documented in writing and provided to the investigators by the Sponsor. This information will be incorporated by the Sponsor when an amendment occurs.

11 Publication Policy

A 'Publication Agreement' will be signed between the Principal Investigator and the Sponsor (if applicable).

If such a Publication Agreement is not signed by both parties as a separate agreement but as part of an overall Clinical Trial Agreement, the publication policy should be part of the Clinical Trial Agreement.

For more information on publication guidelines, please refer to the International Committee of Medical Journal Editors (ICMJE) on www.icmje.org.

12 Investigation Organization

12.1 Investigation Management / Sponsor

The organization, which takes responsibility for the initiation and/or implementation and coordination for the investigation is St. Jude Medical Cardiology Division Inc. d/b/a St. Jude Medical, Cardiovascular Division, Inc. with a principal place of business at 177 East County Road B, St. Paul, MN 55117 and with offices associated with the operation of this investigation located at: 5050 Nathan Lane Plymouth, MN 55442.

SJM will delegate responsibilities to the local SJM clinical entities in each country, as defined by the Power of Attorney.

Sponsor Responsibilities

Sponsor's responsibilities are in accordance with applicable guidelines, covering the design, overall conduct, analysis and reporting of the results of the study. This includes but is not limited to the following activities:

- Perform those actions necessary to protect the rights of subjects and the scientific credibility of the manner in which this study is conducted;
- Select qualified study Investigators, study monitors and research staff;
- Sign off the clinical investigational plan before the start of the investigation or after modifications to the CIP;
- Develop the study database;
- Train the clinical investigational sites;
- Activate the sites after receipt of the required documentation;
- Monitor the participating centers by reviewing collected data and investigation documentation for completeness and accuracy;
- Perform data analysis (SJM reserves the right to obtain data clarification and/or additional medical documentation on subjects enrolled in this study at any time during the subject participation and until the study is terminated or closed by study final report. An interim analysis may be completed at the discretion of the Sponsor);
- Review the investigator´s assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device;
- Report or ensure reporting of all serious adverse events to the EC by the Principal investigator(s), if required by the EC, by national regulations or by the CIP;
- Report all serious adverse events to regulatory authorities within the required time period, if required by national regulations or by the CIP;
- Maintain an updated list of principal investigators, investigational sites and institutions. This list shall be available upon request;

- Design revision controlled CRFs and Patient Information Sheet / Patient Informed Consent form templates;
- Obtain signed Study Agreements and completed Investigator Financial Disclosure information;
- Collect EC approval letters, including a copy of the approved information sheet and consent forms;
- Archive all correspondences relating to the conduct of this study between SJM and the study site, ECs, and Study Monitors;
- Collect CVs and professional licenses for all study personnel, if applicable;
- Obtain protocol/device related training records for all applicable study personnel;
- Collect site personnel signatures and documentation of the Investigator's delegation of study related responsibilities;
- Collect a list of EC voting members;
- Provide insurance certificates.

12.2 Clinical Investigators

All parties participating in the conduct of the clinical investigation shall be qualified by education, training or experience to perform their tasks and this shall be documented appropriately.

The role of the Principal Investigator is to implement, supervise, and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety, and well-being of the subjects involved in the clinical investigation.

All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation.

The Principal Investigator shall;

1. Be qualified by education, training and experience to assume responsibility for the proper conduct of the clinical investigation.
2. Principal investigator and investigation team members shall provide signed and dated CVs and other relevant documentation,
3. Be experienced in the field of application and documented training of investigational device use under consideration,
4. Disclose potential conflicts of interest, including financial disclosure,
5. Be knowledgeable with the method of obtaining informed consent.

Investigator's responsibilities

By agreeing to this Clinical Investigation Plan, the investigators accept to allow monitoring, audits, Ethics Committee review, and regulatory inspections that are related to the investigation. They also agree to provide authorized individuals with direct access to source data and documentation as well as the right to copy records, provided such activities do not violate subject consent and subject data confidentiality.

A Principal Investigator should have experience in and/or will be responsible for:

- Providing signed Clinical Trial Agreement and appropriate appendices; as wll as other study specific agreements;
- Providing the Sponsor with copies of any clinical-investigation-related communications between the Principal Investigator and the EC;
- Screening and selecting appropriate subjects;
- Providing appropriate Ethics Committees Approved Patient Informed Consent;
- Conducting the clinical investigation in accordance with the signed agreement with St Jude Medical, the investigation plan, all applicable laws and regulations, and any conditions of approval imposed by the appropriate Ethics Committees or applicable regulatory authorities where the investigation is performed;
- Collecting and archiving of source data obtained prior to procedure, during procedure, at follow-up examinations and after the investigation has been completed;
- Strict adherence to the CIP testing requirements to provide for optimal safety and efficacious use of the device under clinical investigation;
- Adequate safety reporting;
- Supporting the monitor, and auditor, if applicable, in their activities to verify compliance with the CIP, to perform source data verification and to correct the case report forms where inconsistencies or missing values are identified;
- Notifying the Sponsor of any deviations from the protocol
- Sign off the final version of the clinical investigation plan and amendments to the CIP

It is acceptable for the Principal Investigator to delegate one or more functions to an associate or co-investigator, however, the Principal Investigator remains responsible for the proper conduct of the clinical investigation, complying with the investigational plan and collecting all required data. This delegation of specific functions shall be documented on the Signature and Delegation List (provided by Sponsor). The investigation is not transferable to other centers attended by the investigator unless prior approval is obtained from SJM.

Clinical Coordinating Investigator

In addition to the responsibilities of the investigators, the Clinical Coordinating Investigator will:

- Sign off the final version of the investigational plan and after modifications to the CIP;
- Act as main contact for all investigators in case of medical questions related to the conduct of the investigation.

The following investigators have been appointed by the Sponsor as the Clinical Coordinating Investigators:

Prof. Dr. med. Gerhard Hindricks
Herzzentrum Leipzig GmbH
Abteilung für Rhythmologie
Strümpellstraße 39
04289 Leipzig
Germany
Tel +49 341 865 1421

PD Dr. med. Christopher Piorkowski
University of Dresden, Heart Center
Fetscherstrasse 76
01307 Dresden
Germany
Tel: +49 351 4501901

Participating Sites

The study is planned to be conducted in two German centers (Heartcenter Leipzig, PI: Prof. G. Hindricks; Heartcenter Dresden, PI: PD Dr. med. C. Piorkowski) and one Russian center (State Research Institute of Circulation Pathology, PI: Prof. E. Pokushalov, Novosibirsk, Russia).

12.3 Outsourcing of duties and functions

The sponsor may transfer any or all of the duties and functions related to the clinical investigation, including monitoring, to an external organization (such as a CRO or individual contractor), but the ultimate responsibility for the quality and integrity of the clinical investigation shall reside with the sponsor. All requirements applying to the sponsor shall also apply to the external organization inasmuch as this organization assumes the clinical-investigation-related duties and functions of the sponsor.

12.3.1 Power of Attorney (POA)

The POA delegates sponsor's responsibility for specified tasks to the country entities, divisions or designee, involved in the clinical project. The POA is signed and dated by appropriate parties. The POA can consist of, but is not limited to:

1. Ensure that the clinical agreements are prepared appropriately, comply with legal obligations and are signed/dated by all parties;
2. Ensure that essential documents to activate the center are collected and maintained in the ISB;
3. Activate the centers and manage the centers throughout the duration and close of the investigation;
4. Report Adverse Events to relevant authorities
5. Ensure that subject data relevant to the investigation is referenced in the hospital records, collected and provided to Sponsor

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Appendix A: Office Blood Pressure Measurement

Office Blood Pressure Visits: Baseline, Discharge, 1M, 6M, 12M, 24M

Office blood pressure corresponds to the blood pressure measured by the doctor or the nurse/staff in the office or in the clinic during the subject visit.

Operating Procedures

Subject Instruction:

- Avoid caffeine, exercise and smoking at least 30 minutes prior to the blood pressure measurements

Administrator Instructions:

- Allow the subject to sit quietly for at least 5 minutes in a chair, with feet on the floor before beginning the blood pressure measurements.
- The subject's arm should be supported.
- Have the cuff at the heart level of the subject
- Blood pressure measured with a validated device to identify systolic and diastolic BP. Take three blood pressure measurements (ESC/ESH minimum of two) spaced by 1 to 2 minutes and record the measured values into the worksheet.
- The average of these three measured values determine the office blood pressure of the subject at this visit

Appendix B: 24 Hour Ambulatory Blood Pressure

The standard 24-hour ambulatory blood pressure Visits: Baseline, 6M, 12M, 24M

In the 24-hour blood pressure monitoring, the blood pressure of patient will be measured every 30 minutes during the daytime and every 60 minutes during the night time.

Operating Procedures (ESC and ESH Guidelines)[27]

Patient Instructions:

- Engage in normal activities, but to refrain from strenuous exercise during the measurements
- Keep the arm extended and still during cuff inflations
- Record into the 24-Hour Ambulatory Blood Pressure Recording Log any unusual events that may occur during the 24-hour monitoring

Administrator Instructions:

- Set-up the time interval of automatic blood pressure measurement for patient during the visit
- Ensure that at least two measurements per hour are taken during the person's usual waking hours (for example, between 08:00 and 22:00).
- The average value of at least 14 measurements taken during the person's usual waking hours should be used for calculation of mean.
- Ensure that at least one measurement per hour is taken during the person's usual sleeping hours (for example, between 22:00 and 8:00).
- The average value of at least 8 measurements taken during the person's usual sleeping hours should be used for calculation of mean.

Appendix C: NYHA Assessment Classifications[28]

NYHA Assessment will be evaluated at baseline, 1M, 6M, 12M and 24M follow-up visit and should be classified based on the following definitions:

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Appendix D: Patient Information Sheet and Consent Form Template

PATIENT INFORMATION SHEET AND CONSENT FORM

Full title:
Study Location:
Principal Investigator:
Sponsor: St. Jude Medical Cardiology Division, Inc. d/b/a St Jude Medical Cardiovascular Division, Inc.

1. Introduction

You are invited to take part in a research study because you have high blood pressure that is difficult to treat with medication. The research project is testing a device and a treatment for high blood pressure. The treatment is called renal denervation.
This Patient Information Sheet and Consent Form tells you about the research study. It will explain the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully and ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this study is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether you take part or not.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent to take part in the research project;
- consent to have the tests and treatments that are described;
- consent to the use of your personal and health information as described.

You will be given a copy of this Patient Information Sheet and Consent Form to keep.

2. Purpose and Description of the Research

Your doctor has recommended that you undergo radiofrequency ablation procedure for the treatment of your heart rhythm abnormality (atrial fibrillation). This is the condition where upper chambers of the heart (atria) beat irregularly and rapidly. Your doctor believes that this abnormality is due to electrical impulses traveling improper pathways in your heart. In such cases it has been shown that the cardiac problems can usually be resolved by interrupting those improper pathways. The RF (radio frequency) ablation catheters are used to interrupt those pathways by destroying the responsible abnormal tissue and that is why your physician recommends them for the treatment of your disease.

The purpose of this study is to collect information regarding the effectiveness of a procedure used to treat high blood pressure at the same time as you are being treated for your atrial fibrillation. The procedure is called renal denervation. It involves placing a catheter (long thin round solid tube capable of conducting radiofrequency energy) in your renal (kidney) artery and heating the tip of the catheter to damage the tissue in particular areas of the artery. This tissue is known to contribute to high blood pressure. Previous studies have shown that this treatment may be effective in lowering blood pressure and reducing the recurrence of atrial fibrillation. However, more clinical data is required to confirm these results.

The sponsor of the study is the maker of the device that will be used for the renal denervation procedure. The EnligHTN Renal Denervation System, has been approved for use, and is commercially available. None of the tests and procedures in this study are experimental.

Up to 100 patients will take part in the project at up to 5 centers located in Europe. All patients who are eligible and have the appropriate artery anatomy will have the renal denervation procedure.

Your participation in this study will be approximately 2 years. This study will collect data from you medical history including past treatment for your atrial fibrillation, your high blood pressure, the cardiac ablation and renal denervation procedures, and follow-up study visits.

3. Randomization

You will be “randomized” into a group that will undergo cardiac ablation to treat your atrial fibrillation and a procedure for renal denervation, or else a group that will undergo just ablation for your atrial fibrillation. Randomization means that you are put into a group by chance. No one, including you, the study sponsor, nor the study doctor will choose or will know ahead of time what group you will be in. It is like flipping a coin. You will have an higher chance (67%) of being placed the cardiac ablation plus renal denervation group

4. Study Tests and Procedures

If you agree to participate, the investigator will record your current medications and blood pressure measurements, demographics, ECG and physical assessment for height and weight. The doctor will also complete a NYHA assessment, which is an evaluation to rank the limitations in your daily activities based on shortness of breath and chest pain.

Your doctor will need to confirm your blood pressure. You may be asked to wear a 24 hour blood pressure recording device. This test involves taking your blood pressure at 30 minute intervals throughout the day and at 60 minute intervals during the night using a portable monitor. The monitor itself is a small box approximately 3cm x 11cm x 9cm in dimension. The monitor is worn on a belt around your waist and there will be a tube connecting the box to a cuff which is worn on your arm. The monitor automatically inflates every 30 minutes during the day (or every 60 minutes during the night) over 24 hours. When the cuff begins to inflate you are required to keep your arm extended and still until the cuff deflates. You will also be asked to record unusual events during these 24 hours on a log. It is advisable that you arrange to wear the monitor on a day when you can go about your usual activities, including attending work but refrain from doing strenuous exercise. You will not be able to shower or bathe until the monitor is removed the following day. It is important to return the monitor at this time.

You will also be asked to complete a Quality of Life Questionnaire to assess your general wellbeing, and to provide a blood sample (about 10-15mL) and urine sample to measure how well your kidneys are working. You will be asked not to eat or drink anything except water after 10 pm the night prior to the visit.

You will have an echocardiogram (TTE) and may experience some discomfort from the echo transponder (wand) pushing on your chest during the echocardiogram test. You may be asked to hold very still, breathe in and out very slowly, hold your breath, or lie on your left side during an echocardiogram. You will not have pain during this procedure; however, you may feel uncomfortable from lying still or from the transducer (a small instrument that looks like a microphone) being pressed firmly against your chest to obtain pictures of your heart. Although most people do not experience any discomfort from ultrasound tests, if you have severe difficulty breathing or cannot lie flat for a long examination, please talk to your doctor or the technician performing your procedure about any concerns you have.

You will have a test to assess the structure of your renal arteries. You may have a painless Abdominal Ultrasound, a Computed Axial Tomography (CT) scan, a Magnetic Resonance Angiogram (MRA) or an Angiogram to assess your renal arteries. The following helps explain each test:

- If you have an Abdominal Ultrasound you will be lying down for the procedure. A clear, water-based conducting gel is applied to the skin over the abdomen. This helps with the transmission of the sound waves. A handheld probe called a transducer is then moved over the abdomen. You may be asked to change position so that the health care provider can examine different areas. You may also be asked to hold your breath for short periods of time during the examination. The procedure usually takes less than 30 minutes
- A CT scan combines special x-ray equipment to produce multiple images or pictures of the inside of the body. These images of the area being studied can then be examined on a computer monitor. During the test, you will lie on a table that is attached to the CT scanner, which is a large doughnut-shaped machine. The CT scanner sends X-rays through the body area being studied. Each rotation of the scanner provides a picture of the area being studied. In some cases, a dye called contrast material may be used. It may be put in a vein in your

arm to see the area better. The dye makes structures and organs easier to see on the CT pictures. This procedure can take 15 to 30 minutes.

- Most Magnetic Resonance Angiograms (MRA) exams are typically painless. You will be positioned on the moveable examination table. Straps may be used to help you stay still and maintain the correct position during imaging. It is normal for the area of your body being imaged to feel slightly warm, but if it bothers you, notify the radiologist or technologist. It is important that you remain perfectly still while the images are being recorded. MRA exams generally include multiple runs (sequences), each typically a few seconds to a few minutes at a time. The entire examination is usually completed within one hour. If a contrast material will be used in the MRA exam, a nurse or technologist will insert an intravenous (IV) line into a vein in your hand or arm. It is normal to feel coolness and a flushing for a minute or two when the contrast material is injected.
- An Angiogram is a special kind of x-ray. You will receive a local anaesthetic and then a small puncture will be made through the skin into the femoral artery on your upper thigh (groin).With the aid of fluoroscopy (x-ray that uses a fluorescent screen) a thin, flexible tube called a catheter will be threaded to the renal artery. A special dye will be injected through the catheter so the renal artery will show up clearer on the x-ray. You may be presented with a separate consent form that describes the renal artery angiogram procedure in greater detail.

If the structure of your renal arteries is appropriate for the study and you have been randomized to the renal denervation study group, you will continue to have the renal denervation procedure. If the structure of your renal arteries is not appropriate, you will only have the cardiac ablation procedure, and your participation in the study will end.

The cardiac ablation and renal denervation procedures will be performed in accordance with the standard of care at your facility.

After the procedure you will be transferred for observation and you may stay in the hospital overnight. While you are in hospital your vital signs will be recorded continuously and your blood pressure will be recorded every 4 hours after the procedure until discharge or for a maximum of 24 hours. Also, any unfavorable or unintended symptoms or findings you may have (adverse events) will be recorded and treated as appropriate.

Prior to discharge from hospital your blood pressure and the medications you are taking will be recorded.

After the ablation procedure, you will return for a follow-up visit at 1 month, 3 months, 6 months, 12 months (1 year), and 24 months (2 year),

During your follow up visits the following tests/assessments will be performed:

- Physical Assessment and medication review at every visit
- Office blood pressure measurements at every visit, except the 3 month visit
- 12-lead ECG at every visit
- 24 hour Ambulatory Blood Pressure at 6, 12 and 24 month visits

- Blood and urine samples will be collected at 6, 12 and 24 month visits. You will be asked to not to eat or drink anything except water after 10pm the night prior to the 6 month visit.
- Echocardiogram (TTE) at the 1, 6, 12 and 24 month visits
- NYHA Assessment at the 1, 6, 12 and 24 month visits
- Quality of Life Questionnaire at 1, 6, 12 and 24 month visits
- Renal artery evaluation at 6, and 12 month visits (if you underwent the renal denervation procedure)
- Wear a 7-Day Holter Monitoring/Event Recorder at 3, 6,12, and 24 month visits

5. Study Related Risks

There are risks, discomforts, and inconveniences associated with any research study that you should consider before deciding to participate in this study. You should talk with the investigator if you have any questions.

Precautions will be taken to ensure that side effects, should they occur, will be acted upon immediately.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. Tell your doctor if you have any problems. Your doctor will discuss the best way of managing any side effects with you.

Having blood taken may cause some discomfort or bruising. Sometimes, the blood vessel may swell, or blood may clot in the blood vessel, or the spot from which blood is taken could become inflamed. Rarely, there could be a minor infection or bleeding. If this happens, it can be easily treated.

The cardiac ablation and renal denervation procedures both use an interventional approach, and as such carries some potential risks, which may include but are not limited to the following:

- Visual problems
- Respiratory problems
- New or worsening of existing heart rhythm abnormalities,
- Hypersensitivity reactions,
- Anemia,
- Allergic reactions to anesthesia or other substances,
- Inflammation of the inner (endocarditis) or outer (pericarditis) lining of the heart or heart valves,
- Damage to the heart valves and/or their supporting structures; bleeding, bruising or swelling at the site of catheter insertion (hematoma)
- A hole in or through the heart with bleeding into the sac that surrounds the heart (tamponade),
- Blood clots in the vein, artery, or cavity of the heart (thrombus)
- Occlusion of a blood vessel by an particles that has broken away from a thrombus (thrombo-embolism) or air

- stroke and stroke like events that last for a short time (called Transient Ischemic Attacks or reversible mini-stroke)
- Chest, neck or groin pain
- General feeling or indisposition caused by the procedure,
- Damage to cardiac structure resulting in abnormal heart rhythm or inability to pump enough blood to avoid congestion in tissues
- Painful contraction of heart muscles
- Damage to or dislocation of any cardiac implants
- Dizziness
- Death
- Damage to esophagus
- Motoric aphasia
- Inadequate blood flow to heart muscles (cardiac insufficiency)
- Accumulation of blood in the space between the lungs and the chest wall (hemothorax)
- Oxygen deficiency (hypoxia)
- Elevated PK level
- Fluid or blood build-up around the heart (pericardial effusion) or lungs (pleural effusion)
- Infection or sepsis
- Laceration (cuts and wounds)
- Myocardial Infarction
- Palpitation
- Bradycardia
- Decompensated heart failure
- Pneumonia
- Abnormal presence of air in around lungs resulting in the collapse of the lung; penumothorax)
- Collection of blood in the lining of the vessel wall and the development of a false pouch in the vessel wall (pseudoaneurysm);
- Swelling due to excessive fluid in the lungs (pulmonary edema);
- Radiation damage
- Skin burns
- Fainting (syncope)
- Damage to blood vessels
- Vasovagal reaction
- Vasospasm
- Vasovagal episodes
- Worsening of chronic obstructive pulmonary disease resulting in decreased respiratory function.
- Acute renal injury (renal infarction, renal hematoma)
- Renal vascular injury (renal artery dissection, renal artery thrombosis, renal artery stenosis)
- Collateral tissue injury
- Malignant or accelerated hypertension
- Symptomatic hypotension
- Access site complications (arteriovenous fistula, access site thrombosis, embolisation, pseudo-aneurysm, hematoma, limb ischemia, femoral nerve injury, or seroma)
- Disseminated intravascular coagulation
- Renal failure

- Neurologic event (acute ischemic or hemorrhagic brain injury)
- Pain, including Back Pain
- Death
- Drug reactions
- Contrast allergies etc

When you have CT scan or renal artery angiogram, you will be exposed to radiation. This research study involves exposure to a small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is about 25 mSv. The dose from this study is comparable to that received from several computed tomography x-ray (CT) and nuclear medicine procedures. The benefits from the study should be weighed against the possible detrimental effects of radiation, including an increased risk of fatal cancer. In this particular study, the risk is moderate and the estimated risk of such harm is about 1 in 800. For comparison, this risk is about 200 times lower than the cancer mortality rate in the general population of about one case in every four people.

The effects of renal denervation procedure on the unborn child and on the newborn baby are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you may be required to undergo a pregnancy test prior to commencing the research project.

If you do become pregnant whilst participating in the study, you should advise your treating doctor immediately.

There may be other risks that are not known at this time. Tell your doctor immediately about any new or unusual symptoms that you get.

6. Potential Benefits

We cannot guarantee or promise that you will receive any benefits if you participate in this study. However, if you are randomized to the renal denervation arm of the study, you may experience a decrease in your blood pressure which may have beneficial effects on your heart or less chance of your arrhythmia recurring. Previous studies of renal denervation have reported varying results. One randomized trial using a different product and conducted in the United States, showed no benefit in blood pressure reduction. The RD+AF trial uses a different product and aims to study the impact of renal denervation on your atrial fibrillation. The information gathered from the study will add to the understanding of the treatment options for patients with atrial fibrillation and high blood pressure. This knowledge may benefit future patients.

7. Alternative Therapy

An alternative would be for you to undergo the cardiac ablation treatment for your atrial fibrillation without the chance of a renal denervation procedure taking place at the same time. Your attending doctor will discuss with you the form of treatment most suitable for you. A decision to not take part in the study will not affect your treatment or cause any disadvantages to you.

8. Insurance

All patients will have insurance to cover for economic loss due to health damage as a result of the study. Unless an emergency demands it, any other medical treatment during the duration of the clinical examination should only be undergone after consultation with the examination physician. The clinical examiner must be informed, without delay, of any emergency treatment. When health damage due to the study is being suspected, you are obligated to report this situation to the insurance company immediately. Should death occur, the insurance company must be informed by the legal successors (heirs) within 48 hours. Otherwise, there is a risk of losing the insurance coverage. You may notify the insurer yourself, or you may simply inform the examining doctor who will then inform the insurance company on your behalf. You will receive a copy of this notification from the examining physician. The insurance was contracted with:

ACE Insurance S.A.-N.V., Lurgiallee 10, 60439 Frankfurt/Main (Phone: 069-756130, Fax 069-746193). The insurance number is 43 GW 551024.

The extent of the insurance for a test subject is € 500,000.00.
Damages or aggravation of existing conditions, which also would have occurred or continued without the participation in the study, genetic damage, as well as damages based on the trial person's deliberate failure to follow express instructions in connection with the study, are excluded from insurance.

9. Confidentiality/Data Security

Your data is collected and evaluated exclusively for the purpose of this study. All files and data regarding your participation in this study are dealt with in the context of the applicable laws.

All personal data are subject to the doctor-patient privilege and will not be passed on. Only encoded (pseudonymized) data are passed on to the originator of the study. Only the responsible examining doctor can trace the encoded data back by means of a patient list.

Your data is processed, used, and archived on questionnaires and electronic data carriers for 15 years. All regulations and laws relative to data security will be observed. However, the law provides that your personal and medical data may be recorded and passed on in pseudonymized form to the respective regulatory authorities or responsible Federal authority for the purpose of checking the proper implementation of the study. The data collected shall be made available to the originator of the study in pseudonymized form; i.e. without revealing your name to third parties. During the examinations/check-ups, representatives of St Jude Medical, who are bound by a confidentiality agreement, may be present during the documentation of all data. The information collected from this study is passed on to St. Jude Medical and will be combined with the results of other patients. The results of the study may be published, but your identity will not be revealed. In order to check the study data, it may be necessary for the Information Manager at St. Jude Medical and/or the personnel of the health authorities to access your file. The information gleaned may be published in pseudonymized form in scientific journals or at scientific conferences without the possibility of tracing the data back to you.

10. Compensation (medical/financial)

You will not be paid for taking part in the study. However, you will not be charged the costs specifically related to the study. The costs not specifically related to the study will be charged and reimbursed as usually by your health care coverage. .

11. Study Questions

We hope this answers your questions concerning the proposed evaluation, but if you have any questions about this research you should contact your doctor ("the Investigator") (tel:_____) or the Hospital department. If you have questions about your rights as a research subject you should contact the Ethics Committee at [*telephone #*]. You can also write to the Ethics Committee at [*address*].

12. Study Withdrawal

Your participation in the study is entirely voluntary. If you decide to participate, you may quit the study at any time without a reason. Just tell your doctor you do not wish to continue your participation. If you leave the study before the final regularly scheduled visit, you may be asked by the study doctor to make a final visit. It is recommended you continue to see your regular doctor. There will be no penalty or loss of any benefits to which you are otherwise entitled if you decide not to continue with the study. When you withdraw from the study, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others as described in this form Your doctor or SJM may also stop your participation at any time, without your consent, due to medical conditions or other factors that affect your study eligibility.

13. New Findings

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information and your doctor will discuss whether this new information affects you.

Patient Informed Consent (PIC) Template

Full title: RDN + AF
Study Location:
Principal Investigator:
Sponsor: St. Jude Medical Cardiology Division, Inc. d/b/a St Jude Medical Cardiovascular Division, Inc.

Are you currently participating in other research studies? ___Yes ___No

Statement of Informed Consent:

- I understand that my participation in this study is voluntary
- I understand that I am free to refuse to participate in this study without giving reason and without my medical or legal rights being affected
- I understand that I am free to withdraw from this study at any time without giving reason and without my medical care or legal rights being affected.
- I understand that data collected during this study prior to the withdrawal will be used in the analysis and communicated in publication.
- I understand that information gained during the study maybe published, and I will not be identified and personal data will remain confidential.
- I understand that my health information may be stored in a database and study results may be looked at, used, and disclosed by the investigators, St. Jude Medical, Cardiology Division, Inc. d/b/a (doing business as) St. Jude Medical, Cardiovascular Division, Inc., a U.S. company, and its affiliates (located in the USA and European Economic Area and other countries), and other people who work for St. Jude Medical to provide services related to the device and this study (SJM) regulatory authorities, and the Ethics Committee, when it is relevant to my taking part in this research. I give permission for these individuals to have access and use to my medical information for this study.
- I understand that photograph and video recordings (after being anonymised) may be taken during the operation of the device during the study and used for this study and future research.
- I understand that my information will not be used for any mailing lists or sold to anyone for marketing purposes.
- I understand I have a right of access and a right to correct any inaccuracies in information about me .
- I understand the risks associated with this study.
- I understand that I may not benefit from taking part in the study.
- I understand that this study was reviewed by the Ethics Committee.
- I understand how to contact the research team if I have concerns about the study

Acknowledgement of the information provided:

- I confirm that I have read and understood the information presented for this study.
- I have had the opportunity to discuss participation in the study and have had the opportunity to ask questions and have them answered.

Informed Consent Agreement:

- I agree to participate in this study and to comply with the procedures related to it.
- I give my permission to have my general practitioner informed of my participation in this study.
- I give my permission to access my records by the investigator, sponsor(and its designees), ethics committee, and regulatory authorities for data for the purpose of this study.

Subject Signature

Subject Signature _____ Date_____

Printed Name of Subject _____

Subject's Legal Representative (if necessary) Signature

Signature _____ Date_____

Printed Name of Legal Representative_____

Person Conducting Informed Consent Discussion

Signature _____ Date _____

Printed Name _____

Appendix E: Abbreviations

Abbreviation	Term
ABP	Ambulatory Blood Pressure
ADE	Adverse Device Effect
AE	Adverse Event
ANZ	Australia – New Zealand
ASADE	Anticipated Serious Adverse Device Effect
BP	Blood Pressure
CA	Competent Authority
CCI	Clinical Coordination Investigator
CIP	Clinical Investigational Plan
CRF	Case Report Form
CPRB	Clinical Project Review Board
CT	Computed Axial Tomography
DCC	Data Cleaning Convention
DD	Device Deficiency
DMP	Data Management Plan
DVP	Data Validation Procedure
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMEAC	Europe, Middle East, Africa, Canada
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GP	General Practitioner
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
ISB	Investigator Site Binder
ISO	International Organization for Standardization
MDRD	Modification of Diet in Renal Disease
MP	Monitoring Plan
MR	Magnetic Resonance
NAP	Not Applicable
PI	Principal Investigator
POA	Power of Attorney
RDC	Remote Data Capture
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SJM	St. Jude Medical
USADE	Unanticipated Serious Adverse Device Effect
WMA	World Medical Association

Appendix F: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

- The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
- The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
- Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

- It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

- The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

- Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

- In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

- The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and

therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

- In medical practice and in medical research, most interventions involve risks and burdens.

- Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

- It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

- Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

- Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

- The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, and other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

- The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

- Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

- Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

- Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

- Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

- Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

- Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

- Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

- Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

- In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

- For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

- When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

- For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

- When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to

the consent of the legally authorized representative. The potential subject's dissent should be respected.

- Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

- Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

- The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

- The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

- At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example,

access to interventions identified as beneficial in the study or to other appropriate care or benefits.

- The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

- In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Appendix G: Data Collection Method (EDC)

Sponsor/Investigators are required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each subject. Source documents include all original records from which eCRFs derive their data.

Access to eCRF application

The eCRF application is accessed through the internet and requires the use of a personal user account and password.

The following documents and information are required prior to receipt of personnel user account and password:

- Current signed and dated CV
- Completed Signature and Delegation List
- Documented training
- Email address and telephone

Personal user account and password are provided via email. User account and password are confidential and personal. They are not to be shared with other people.

The first time the application is accessed, the password will need to be changed.
If the password is forgotten and/or lost, a new password can be provided via email by following the instructions on the webpage.

Each center must be authorized to start enrolling patients in the investigation before access privileges to the application is made available.

Access privileges are based on the tasks assigned on the Signature and Delegation List and will be either:

- Data entry and review
- Data entry, review and sign off

All eCRFs are completed, saved (‘save complete’) and approved by an investigator in a timely manner.

Appendix H: List of Case Report Forms

Data Points Provided Under Separate Cover

- Screening: Inclusion/Exclusion Criteria
- Baseline/Medical History Form
- Physical Assessment/Office Blood Pressure Form
- 24 Hour Ambulatory Blood Pressure Form
- Echocardiography Form
- Blood/Urine Lab Form: Serum Creatinine, eGFR, Hemoglobin A1c, Fasting Glucose, Fasting Insulin and Albumin-Creatinine Ratio
- Renal Artery Evaluation Form
- Procedure Form
- Post Procedure and Discharge Form
- AF Recurrence Form
- Adverse Event Form
- Death Form
- Deviation Form
- Termination Form