# QDOT – nGEN

## Acute Performance Evaluation of the QDOT Micro™ Catheter used with nGEN Generator in Treatment of Patients with Atrial Fibrillation.

| | |
|---|---|
| Protocol Number: | BWI_2019_09 |
| Sponsor/Company: | Biosense Webster, Inc., a division of Johnson & Johnson with registered office at [redacted] |
| Funded by: | Biosense Webster, Inc., part of the Johnson & Johnson family of companies. |
| Version: | v.4.0 |
| Date: | 02 Mar 2021 |

TABLE OF CONTENTS

## List of Tables



## List of Figures

## List of Acronyms and Abbreviations

| Acronym/ Abbreviation | Expanded Term |
|---|---|
| AAD | Antiarrhythmic Drug |
| ACC/AHA | American College of Cardiology/American Heart Association |
| ACT | Activated clotting time |
| AE | Adverse Event |
| AEF | Atrio Esophageal Fistula |
| AF | Atrial Fibrillation |
| AFL | Atrial Flutter |
| AT | Atrial Tachycardia |
| BP | Blood Pressure |
| CA | Competent Authority |
| CABG | Coronary Artery Bypass Graft |
| CE | Conformite Européen |
| CHF | Congestive Heart Failure |
| COPD | Chronic Obstructive Pulmonary Disease |
| CPK | Creatinine Phosphokinase |
| CRF | Case Report Form |
| CS | Coronary Sinus |
| CT | Computed Tomography |
| CVA | Cerebrovascular Accident or Stroke |
| DD | Device Deficiency |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EF | Ejection Fraction |
| EHRA AF | European Heart Rhythm Association Atrial Fibrillation |
| EMEA | Europe, Middle East and Africa |
| EOS | End of Study |
| EP | Electrophysiology |
| ER | Emergency Room |
| ESC | European Society of Cardiology |
| EU | European Union |
| FAM | Fast Anatomical Mapping |
| FU | Follow-Up |
| GCP | Good Clinical Practices |
| GI | Gastro-Intestinal |
| HRS/EHRA/ECAS | Heart Rhythm Society / European Heart Rhythm Association / European Cardiac Arrhythmia Society |
| IB | Investigator Brochure |
| ICD | Implantable Cardioverter-Defibrillator |
| ICE | Intracardiac Echocardiography |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| ID | Identification |
| IFU | Instruction for Use |
| ISO | International Organization of Standardization |
| ITT | Intention to treat |
| IV | Intravenous |
| LA | Left Atrium |
| LBBB | Left Bundle Branch Block |
| LV | Left Ventricle |
| LVEF | Left Ventricular Ejection Fraction |
| MEDDEV | Medical Device Directive |

| Acronym/ Abbreviation | Expanded Term |
|---|---|
| MI | Myocardial Infarction |
| MOH | Ministry of Health |
| MRI | Magnetic Resonance Imaging |
| NOS | Not Other Specified |
| NSR | Normal Sinus Rhythm |
| NYHA | New York Heart Association |
| PAF | Paroxysmal Atrial Fibrillation |
| PsAF | Persistent Atrial Fibrillation |
| PE | Primary Endpoint |
| PI | Principal Investigator |
| PIU | Patient Interface Unit |
| PN | Phrenic Nerve |
| PNP | Phrenic Nerve Paralysis |
| PV | Pulmonary Vein |
| PVI | Pulmonary Vein Isolation |
| QA | Quality Assurance |
| QoL | Quality of Life |
| RA | Right Atria |
| RBA | Risk-Benefit Analysis |
| RF | Radiofrequency |
| RV | Right Ventricle |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SDV | Source Data Verification |
| SVC | Superior Vena Cava |
| SW | Software |
| TEE | Transesophageal Echocardiography |
| TIA | Transient Ischemic Attack |
| TS | Transseptal |
| TTE | Transthoracic Echocardiography |
| UADE | Unanticipated Adverse Device Effect |
| UNS | Unscheduled |
| US | United States |
| USADE | Unanticipated Serious Adverse Device Effect |

## Key roles and Responsible Parties

**SPONSOR:**

**Cardiovascular & Specialty Solutions (CSS)**

Biosense Webster Inc., part of the Johnson & Johnson family of companies

[redacted]

**CONTACTS:**

**Clinical Research Contact, US**

**Bita Najimipour**

[redacted]

**Medical Affairs**

**Jack Wang, MD**

[redacted]

**Clinical Research Contact, CANADA**

Swati Trivedi

Johnson & Johnson Medical Products

[redacted]

Whereas, the Clinical Study is sponsored by Biosense Webster Inc., Johnson and Johnson Medical with registered offices at CANADA, has been duly appointed by the Sponsor to conduct the Clinical Study on its behalf.

The sponsor maintains an updated list of Sponsor study contacts, principal investigators, sites, institutions and Contract Research Organizations (CRO) (if applicable). The definitive list shall be integrated into the study report.

## Statement of Compliance

Study Title: **Acute Performance Evaluation of the QDOT Micro™ Catheter used with nGEN Generator in Treatment of Patients with Atrial Fibrillation.**

History of Changes:

| Version – Date | Description |
|---|---|
| V1.0 – 08 JAN 2020 | Original document |
| V2.0 – 27 JAN 2020 | Administrative changes – Protocol Title Update |
| V3.0 – 27 APR 2020 | Add 3-Month Follow-up Visit |
| V4.0 – 02 Mar 2021 | Product information update<br>Visit assessments update due to COVID-19 |

Study #: BWI_2019_09

I have read this protocol and agree to conduct this clinical investigation in accordance with the design and specific provisions outlined herein. I understand the protocol, and I understand I am solely responsible to ensure the investigation is conducted in accordance with Good Clinical Practices (GCP), applicable country regulations the Declaration of Helsinki, the signed clinical study contract with Sponsor and with the protocol outlined herein. I will conduct this study as outlined therein and will make reasonable effort to complete the study within the time period designated by the Sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

I will fulfill the requirements of my Institutional Review Board (IRB)/Ethics Committee (EC), or other oversight committee, to ensure complete and continual oversight of this clinical investigation. I will use an Informed Consent Document approved by the Sponsor and my reviewing IRB/EC (where required).

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events, device related adverse events, or procedure related adverse events as defined in this protocol to the Sponsor, and comply with all adverse event reporting requirements of my reviewing IRB/EC. I agree to permit the Sponsor, its authorized representatives, my reviewing IRB/EC, and any regulatory authority/body access to all records relating to the clinical investigation.

The below signature confirms I have read and understood this protocol and its associated amendments or attachments and will accept respective revisions or amendments provided by the Sponsor.

| | | |
|---|---|---|
| Principal Investigator | Signature | Date |
| Name (PRINT) | | |

## Protocol Summary

| | |
|---|---|
| **Full Title** | Acute performance evaluation of the QDOT Micro™ Catheter used with nGEN Generator in treatment of patients with Atrial Fibrillation. |
| **Protocol Number** | BWI_2019_09 |
| **Short Title** | QDOT-NGEN |
| **Sponsor** | Biosense Webster, Inc. [redacted] |
| **Indication** | Atrial Fibrillation (Paroxysmal and Early Persistent, diagnosed for ≤6 months) |
| **Study Article Description** | QDOT MICRO™ System, consisting of a radiofrequency ablation catheter combining microelectrodes, thermocouples, porous tip irrigation and contact force sensing with the nGEN Generator with conventional (QMODE) and QMODE+ modality software installed. The QMODE+ modality is designed to deliver very high power (90w) in a short ablation duration (up to 4 sec) under temperature control.<br><br>The nGEN / QDOT Micro Ablation System<br>• nGEN™ Generator (D-1384-01), (console software version 2.0.3 and above /monitor software version 2.0.0 and above)<br>• nGEN™ pump (D-1397-01)<br>• QDOT MICRO™ Catheter (D-1394-XX-S and D-1395-XX-S)<br>  ○ Dongle (D-1401-02)<br>  ○ TX eco EXT Cable (D-1357-03-S)<br><br>CARTO® 3 Version 6.0 or above |
| **Study Design** | The purpose of this study is to evaluate the workflow of the nGEN system with the QDOT Micro™ catheter. Criteria to be assessed: acute performance of the QDOT Micro™ Catheter with nGEN Generator used in the treatment of atrial fibrillation during standard electrophysiology mapping and RF ablation procedures.<br><br>BWI developed the nGEN RF generator with the same electrical design and software algorithm as the nMARQ Generator for use with the QDOT Micro™ Catheter. Accordingly, the essential performance of the nGEN Generator, which include power output and accuracy, temperature accuracy and control to start and stop ablations, are the same or improved compared to the nMARQ Generator. The nGEN Generator has undergone extensive software, hardware, system and preclinical testing to assure safety and effectiveness. Based on the same algorithm and essential performance, the clinical performance equivalency, safety and effectiveness of the nGEN Generator to use with the QDOT Micro™ catheter are established. This study is to obtain additional confirmatory data in the electrophysiology laboratory setting with expanded users.<br><br>The QDOT-nGEN study is a prospective, multi-center, non-randomized, interventional clinical workflow study. |

| | |
|---|---|
| **Sample Size and Statistical Analysis** | Up to 50 subjects with a minimum of 30 subjects undergoing a study ablation procedure will be enrolled.<br>This study is a workflow study, there is no statistical power calculation and no hypothesis will be tested. Descriptive statistics will be presented. Thirty subjects (30) undergoing an ablation procedure are deemed enough to characterize safety and acute performance. |
| **Study Population** | Subjects with AF who are scheduled to undergo a clinically indicated ablation procedure for management of their AF will be the target population for screening. |
| **Geographic areas to be included** | Up to 6 centers in Canada |
| **Study Duration** | Approximately 9 months |
| **Participant Duration** | Subjects will be followed until completion of the 3-month visit post-procedure |
| **Procedure Description** | Subjects will arrive to the electrophysiology laboratory for their ablation procedure and will undergo preparation for the procedure per the hospital's standard protocol (discretion of investigator).<br>The AF Ablation procedure will follow below sequence:<br>• Esophageal monitoring to avoid injury is recommended when ablating near the esophagus<br>• Anatomical mapping of the left atrium<br>• Introduction of the study catheter<br>• Circumferential Pulmonary Vein Isolation (PVI) primarily using QMODE+ mode<br>• Confirmation of PVI with Lasso® or PentaRay® (or other at investigators discretion)<br>• Confirmation of entrance block with adenosine/isoproterenol challenge<br>In this study protocol, QMODE+ is to be used as the primary mode for pulmonary vein isolation. Only after the investigator deems QMODE+ is unable to achieve PVI should the study catheter in QMODE be used to complete the procedure.<br>Additional RF ablation lesion outside the PVs can be made by either QMODE+ or QMODE at the discretion of the physician. |
| **Primary Endpoints** | **Acute Performance**:<br>Acute Procedural Success defined as confirmation of entrance block in all targeted PVs after adenosine and/or isoproterenol challenge using the nGEN / QDOT Micro Ablation System |
| **Additional Data Collection** | **Adverse events:**<br>- Adverse events will be collected and evaluated. All events will be reported to complaints handling unit.<br>**Procedural parameters**<br>- PVI achieved with QMODE+ only among all targeted veins and by subject<br>- PVI achieved with combined use of QMODE+ and QMODE among all targeted veins and by subject<br>- Need for ablation of acute PV reconnection (touch-up) among all targeted veins and by subject<br>- Temperature, power, contact force, impedance<br>- Functionality of nGEN RF generator during PVI assessed by the nGEN data files<br>**Additional analyses on procedural data, including but not limited to:**<br>- Use of QDOT Micro™ catheter ablation of targets outside the PV area |

| | |
|---|---|
| | - Total procedure time, mapping time, PV ablation time, total ablation time, RF application time<br>- Total number of RF applications, % QMODE+ applications and % QMODE applications<br>- Anatomical location of touch-up applications using the QDOT catheter |
| **Subject population** | Subjects diagnosed with symptomatic paroxysmal or early persistent atrial fibrillation undergoing catheter ablation through pulmonary vein isolation |
| **Inclusion Criteria** | Subjects must meet ALL the following inclusion criteria to be eligible for participation in this clinical investigation:<br>1. Subjects diagnosed with symptomatic paroxysmal or early persistent AF undergoing a catheter ablation procedure through pulmonary vein isolation.<br>2. Age 18 or older.<br>3. Signed the Patient Informed Consent Form (ICF). |
| **Exclusion Criteria** | Subjects who meet ANY of the following exclusion criteria are not eligible for enrollment.<br>If a subject meets the following exclusion criteria, they will not be enrolled in the study:<br>1. If the patient has had a ventriculotomy or atriotomy within the preceding twelve weeks.<br>2. Presence of a myxoma or an intracardiac thrombus.<br>3. Presence of prosthetic valves.<br>4. Presence of active systemic infection<br>5. Patient with an interatrial baffle or patch<br>6. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of childbearing age and plan on becoming pregnant during the course of the clinical investigation. |
| **Contraindications** | Do not use this catheter:<br>1. If the patient has had a ventriculotomy or atriotomy within the preceding twelve weeks because the recent surgery may increase the risk of perforation.<br>2. In patients with a myxoma or an intracardiac thrombus as the catheter could precipitate an embolus.<br>3. In patients with prosthetic valves as the catheter may damage the prosthesis.<br>4. In the coronary arterial vasculature due to risk of damage to the coronary arterial vasculature.<br>5. In patients with an active systemic infection because this may increase the risk of cardiac infection.<br>6. Via the transseptal approach in a patient with an interatrial baffle or patch because the opening could persist and produce an iatrogenic atrial shunt.<br>7. Via the retrograde trans-aortic approach in patients who have had aortic valve replacement.<br>8. With a long sheath or short introducer < 8.5 F in order to avoid damage to the catheter shaft. |
| **Safety Monitoring** | All data will be summarized by descriptive analyses. No formal statistical inference will be made. |
| **Time and Events Schedule** | See table 1 below |

**Table 1. Summary of Subject Assessments**

(to be completed 60 days prior to ablation procedure)

| **Assessments** | **Pre-ablation** | **Procedure** | **Pre-discharge** | **7D** (D6-10) | **M3** (D76-104) |
|---|---|---|---|---|---|
| Clinic visit | ● | ● | | | ● [1] |
| Phone Call | | | | ● [1] | |
| Patient Informed Consent[2] | ● | | | | |
| Demographics[2] | ● | | | | |
| Medical/AF history | ● | | | | ● |
| Cardiac and Anticoagulation Medications | ● | | ● | ● | ● |
| Ablation Assessment | | ● | | | |
| ECG | | | ● [5] | ● [1,5] | ● [1,5] |
| Pregnancy Test | ● [3] | | | | |
| LA thrombus detection | ● [2] | | | | |
| Adverse events/Device Deficiency[4] | ● | ● | ● | ● | ● |
| AF Recurrence | | | ● | ● | ● |

1. May be conducted as a clinic visit (ECG performed if Clinic visit) or a telehealth visit.
2. To be completed within 48 hours prior to ablation procedure
3. In all women of childbearing age and potential. To be completed within one week prior to ablation procedure.
4. Device Deficiency to be collected at ablation and pre-discharge
5. If Completed At the investigator's discretion.

# 1. Background Information and Scientific Rationale

## 1.1. Background Information

Atrial fibrillation (AF) is the most common sustained arrhythmia in humans. It affects anywhere from 0.4% to 1% of the general population, and increases in prevalence with age, from < 1% in young adults to 8% in patients over 80 years of age [1-4].

Radiofrequency (RF) catheter ablation has provided excellent results for treating many types of supraventricular arrhythmias [4, 5]. Its utility in treating paroxysmal AF has already been established; studies have shown high rates of elimination of the arrhythmia [6, 7]. In a non-randomized clinical trial evaluating the impact of contact force on successful outcomes, RF ablation with the THERMOCOOL SMARTTOUCH® SF catheter was associated with elimination of symptomatic atrial arrhythmias in 72.5% of patients at 1 year [8].

The 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Consensus Statement states that electrical isolation of the pulmonary veins (PVs) from the left atrium is “the cornerstone for most AF ablation procedures.”[2] Creation of transmural, continuous, and durable RF lesions is the objective of PVI. Conventional parameters of radiofrequency (RF) ablation with irrigated catheters involve the delivery of moderate power (20-40W) for a relatively long duration (20-40sec) at a contact force range of 10-20g. Still, the incidence of acute PV reconnection remains frequent, occurring after PVI at a frequency 15-22%.[8, 9] While the mechanisms underlying PV reconnection are not entirely understood, catheter instability, tissue edema, and reversible non-transmural injury have been suggested as major contributor [10, 11].

RF lesion formation results from two thermal heating phases; resistive and conductive heating. Resistive heating is highly dependent on RF power immediately creating a hot spot ~2mm from the tip. This resistive heating phase creates a heat source that extends passively to deeper tissue layers during the conductive phase. Conductive heating is time dependent, with heat conducted from the hot spot into the deeper layers of the myocardium [12].

Modification of the relationship between the resistive and conductive heating phases, by increasing the resistive heating phase to deliver immediate heating to the full thickness of the LA tissue circumferential to the PVs, may achieve uniform, transmural lesions. By reducing the conductive heating phase collateral tissue damage could be limited [13, 14]. This can be achieved by delivering a large current for a short duration.

The Biosense Webster QDOT MICRO™ catheter is a steerable multi-electrode luminal catheter with a deflectable tip designed to facilitate electrophysiological mapping of the heart and to transmit radiofrequency (RF) current to the catheter tip electrode for ablation purposes. In addition to force-sensing technology, the catheter incorporates six thermocouple temperature sensors and three micro electrodes embedded in the 3.5 mm tip electrode.

The measured temperature can be used by the operator to assess the efficiency of ablation in real time. The localized temperature measurement will provide a highly sensitive measure of catheter location stability and/or movement during RF application and may reduce the need for additional RF applications.

The micro electrodes will provide high quality localized electrograms that will allow finer endocardial electrical mapping and a better assessment of possible conduction gaps in the ablation lesion sets used to isolate the pulmonary veins and determining bidirectional block of linear lesion sets.

Finally, the catheter tip has incorporated a new angled design of the irrigation ports. This new design allows for reduced incidence/risk of charring and coagulum on the catheter increasing safety during the ablation procedure.

The nGEN Generator is used by electrophysiology (EP) Physicians in conjunction with compatible catheters, to deliver RF energy to cardiac tissue to treat arrhythmia. An ablation catheter is connected via interface cables to nGEN Generator or through CARTO 3 System. The nGEN Pump is also connected to nGEN generator via pump/generator communication cable and the appropriate saline flow rate is automatically activated by the generator during ablation. The generator can be configured to support various BWI therapeutic ablation catheter families. The current version is configured for use with the QDOT MICRO Catheter.

Delivery of very high power for short duration (90W, up to 4 seconds) achieves uniform transmural lesions, mainly relying on resistive heating [15, 16]. QMODE+ at 50-90W, up to 4 seconds may significantly shorten RF ablation time while maintaining the effectiveness and safety profile. A temperature limit has been defined (maximal at 65°C) to maintain the ablation safety profile. Ablation effectiveness may be improved since the physician is required to maintain catheter stability for a short duration. By reducing the conductive heating phase, QMODE+ may minimize the risk of collateral damage to adjacent structures.

## 1.2. Rationale for Design of the clinical investigation

### 1.2.1. Previous Experience with QDOT MICRO™ Catheter and Rational

A series of In vivo and in vitro experiments, including thigh muscle preparation model and in vivo beating heart experiments, were conducted to determine an appropriate QMODE+ setting that could be demonstrated to be safe and deliver uniform transmural lesion near the PV circumference. The main objective was to identify and evaluate an optimal ablation setting that allows maximal power output at the shortest duration possible, without char or steam-pop formation. A range of power (i.e. 50-100W) and durations (3-15 seconds) were studied and analyzed. The data from these evaluations suggests that using higher power to promote resistive heating while shortening the duration to limit the impact of conductive heating through adjacent tissue provides the optimal balance for efficiency, effectiveness and safety. The conclusion from these studies has been implemented as the QMODE+ algorithm using ablation parameters of 90W for a duration of 4s (irrigation setting at 8ml/min). These parameters were used for validation of animal studies as summarized in the Investigator Brochure (IB).

Two feasibility studies are conducted to assess the performance of the QDOT MICRO™ Catheter.
The purpose of the QDOT-MICRO study (NCT02944968) was to evaluate the workflow and acute performance, during standard electrophysiology mapping and RF ablation procedures, of the QDOT MICRO™ Catheter with improved temperature sensing capabilities and micro electrodes used in combination with the CARTO®3 Navigation System with QDOT-MICRO Software Module. The CARTO®3 System (Health Canada Licenses 81053 and 91793) is an advanced imaging technology that utilizes electromagnetic technology to create real-time, 3D maps of a patient's cardiac structures, designed to help electrophysiologists better navigate the heart. The CARTO® 3 EP Navigation System is intended for catheter-based atrial and ventricular mapping. The QDOT MICRO study was a prospective, multi-center, non-randomized, interventional clinical study with a target population of paroxysmal AF subjects who were scheduled to undergo a clinically-indicated ablation procedure for management of their paroxysmal AF and a follow up period of 3 months post procedure. In total 51 subjects were enrolled. The conclusion of the study was that the QDOT MICRO™ Catheter and its combined system modalities, in treatment of patients with Paroxysmal Atrial Fibrillation has

demonstrated a favorable acute device performance and safety profile. In addition, based on investigator feedback the design of the catheter and software modalities have acceptable performance.

A second feasibility study namely the QDOT-FAST study (NCT03459196) was previously conducted. The purpose of this feasibility study was to evaluate safety and acute performance of the QDOT Micro™ catheter used in combination with the nMARQ™ Multi-Channel RF Generator with QMODE+ mode in the treatment of Paroxysmal Atrial Fibrillation (PAF) during standard electrophysiology mapping and RF ablation procedures. This was a prospective, multi-center, non-randomized, interventional clinical study with a target population of paroxysmal AF subjects who are scheduled to undergo a clinically-indicated ablation procedure for management of their paroxysmal AF a follow up of 3 months post procedure. In total 54 subjects were enrolled. The conclusion of the study was that the QDOT-MICRO™ catheter used in combination with the nMARQ™ Multi-Channel RF Generator and QMODE+ ablation mode in treatment of patients with Paroxysmal Atrial Fibrillation has demonstrated an acceptable safety and acute effectiveness profile.

This workflow study will further evaluate the acute performance of the QDOT MICRO™ catheter used in combination with nGEN Generator in a patient population within the indication for use, namely in patients with paroxysmal and persistent Atrial Fibrillation during standard electrophysiology mapping and RF ablation procedures. The main objectives of the study are acute device performance and acute safety. The study will enroll up to 50 subjects with a minimum of 30 subjects will be enrolled at 6 centers in Canada. Subjects will be followed for 3 months post procedure.

The QDOT MICRO™ Catheter was licensed on December 18, 2020 under License 105640, whereas the nGEN Generator which has been recently upgraded (console software version 2.0.3 and above /monitor software version 2.0.0 and above) is an investigational device since the upgraded version has not been licensed in Canada.

## 1.3. Potential Risk and Benefit

RF catheter ablation has been used for over 20 years, and the risks and complications are well understood. Procedural risks posed by the QDOT MICRO™ catheter are expected to be comparable to these known anticipated risks [2, 3, 17]. Few, if any, additional risks that might occur during and following RF ablation of symptomatic PAF are anticipated for subjects enrolled in this study.

A summary of risks associated with catheter ablation, including analysis of and plans to minimize these risks is provided below:

### 1.3.1. Known Potential Risks

***Risks associated with catheter ablation***

Studies have reported low rates of major complications (0.8%)[21, 22] with major centers worldwide reporting rates <5% [23, 24] associated with catheter ablation. The most common complications associated with catheter ablation of AF include:

Cardiac tamponade is reported at approximately 0.2 to 5% in catheter ablation of atrial fibrillation (AF) [2], comprising mainly pulmonary vein isolation (PVI) procedures. Data presented by recent meta-analysis of 34,943 ablation procedures by Michowitz et al reported incidence of 0.8% . Rates as low as 0.18% have also been reported in a recent study that reviewed complications among 2,750 procedures [19].

The general incidence of pericardial effusion during AF ablation is around 1.2% to 1.3% [21-31]. Cardiac perforation may result from catheter manipulation or application of radiofrequency current. Published risks of cardiac perforation range from <1%to 2.4% [21]. However the risk of perforation is decreased with advances in catheter technology [23]. This potentially life-threatening injury may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. Significant hemodynamic compromise can result in neurologic injury or death. An increased risk of cardiac perforation may be associated with the use of a saline-irrigated electrode catheter due to its ability to create a larger, deeper RF lesion. This risk is greatest in a thin walled chamber (i.e., RA, LA, appendage, or RV).

**Pulmonary vein stenosis:** Pulmonary vein stenosis (PVS) is a well-known complication of radiofrequency catheter ablation of atrial fibrillation. Incidence of severe PVS (>70% diameter reduction) was found to be <1% in a recent study with 976 subjects [24]. Incidence of only 0.5% was reported in a large systematic review on complications of radiofrequency catheter ablation.

**Esophageal injury:** Since the left atrium has close anatomical proximity to the esophagus, catheter ablation on the LA posterior wall may thermally damage the esophagus and eventually generate an esophageal ulcer with a prevalence of 5% [25] that rarely progresses to an atrial esophageal fistula (AEF) with catastrophic consequences [26]. Esophageal injury by endoscopy has a prevalence between 2.2 to 21% [25]. Esophageal perforation is a serious complication of atrial fibrillation ablation that occurs in 0.02 to 11% [25, 27] of atrial fibrillation ablation procedures. Delayed diagnosis is associated with the development of atrial-esophageal fistula (AEF) and increased mortality. Complication rates for esophageal injury are quite varied, depending upon lesion location and type of lesion found (erythema, necrotic ulceration, perforation, or fistula formation). The incidence of AEF post-ablation of AF is approximately 0.1% [28]. Studies using luminal temperature monitoring to identify potentially dangerous heating of the esophagus during ablation have not been able to demonstrate reduction in incidence [29].

**Phrenic nerve paralysis:** Currently, this complication has been reported in less than 0.5%, with permanent paralysis between 0% to 0.4% when the isolation of right PV is not obtained during PV antra isolation and RF ablation is performed inside at carina the right PVs [2, 29, 30]. A 2018 published study reported very low rates of PNP of 0.04% among 2,750 procedures [19]. Prior to ablation in the region of the RSPV, investigators are encouraged to perform precautionary measures such as evaluation of proximity to the phrenic nerve and pacing maneuvers.

**Death** is an uncommon complication associated with CA techniques. Overall incidence of death has been reported to be <0.1% to 0.4%[2]. A 2010-published global survey provided an overall mortality rate of 0.1%. Another report from an international survey of AF ablation of 162 centers provided details on 32 deaths that occurred during or after AF ablation procedures in 32,569 patients (0.1%) [31, 32]. Among the most frequent causes of death were cardiac tamponade (25% of deaths), stroke (16%), atrio-esophageal fistula (16%) and massive pneumonia (6%) [31].

Radiofrequency current may cause occlusion of a coronary artery, either by direct thermal damage, spasm, or thrombus formation. Acute coronary artery occlusion is a very rare but potentially life-threatening complication of RFCA [33]. Experience at numerous centers suggests that the risk of coronary occlusion is less than 0.5% [34]. Coronary arterial occlusion could produce myocardial infarction (MI), angina or death. Occlusion of a coronary artery can be treated by restoring coronary blood flow through pharmacological, catheter and/or surgical intervention as medically indicated.

The application of radiofrequency current close to the AV node or His bundle could damage or destroy the normal AV conduction system, producing complete heart block and requiring implantation of a permanent pacemaker.

**Thromboembolic events:** Thrombus generation during the procedure may pose a serious and even life-threatening risk to the patient. Thrombus may form on the ablation electrode during the application of radiofrequency current with or without any change in impedance. The thrombus might become dislodged and embolize to produce an ischemic stroke, MI, or other occlusive injury. Although some observational studies have shown a relatively lower stroke rate after catheter ablation, whether catheter ablation can reduce the thromboembolic risk remains unclear.

The mean incidence of thromboembolism associated with AF ablation was reported by Cappato et al in 2010 to be between 1% and 2% [21]. More recently, Fujii et al have reported incidence of thromboembolism in up to 5% of patients undergoing AF ablation despite perioperative anticoagulation [35]. Ischemic stroke events typically occur within 24 hours of the AF ablation procedure with the higher risk period covering for the first two weeks following ablation [36].

**Pulmonary hemorrhage** is a rare but severe complication of PVI. Late hemoptysis and pulmonary hypertension can occur secondary to pulmonary vein stenosis (PVS) after ablation. Acute pulmonary hemorrhage also has been reported[37]. Mechanical trauma from catheter manipulation is a possible mechanism for pulmonary hemorrhage [41] .

Injury to a cardiac valve may result from catheter manipulation or the application of radiofrequency current (risk <1%) [38][42]. This may produce valvular insufficiency and possibly require valve replacement surgery.

**Vascular access / bleeding complication:** Arterial or venous injury, including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other sites along the vessels (risk 0.2% to 1.5%) [2, 39, 40]. These types of injuries may cause hemorrhage, hematoma or ischemic injury to an extremity or major organ.
Hemorrhage could occur as a result of anticoagulation (risk < 0.5%), which may require transfusion [43,44].

**Radiation exposure:** Radiation exposure during the fluoroscopic imaging of the catheters may result in an increase in the lifetime risk of developing a fatal malignancy (0.1%) or a genetic defect in offspring (0.002%) [41-43].

**Allergic Reaction**: A patient could develop an allergic reaction to the local anesthetic, sedatives, x-ray dye, heparin, protamine, or other agents administered during the procedure (risk < 1%) [44-48].

**Infection:** The percutaneous procedure carries risk of infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk < 0.5%) [39, 40]. This risk can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents.

**Additional contraindications:** Additional contraindications for RF ablation include: hemodynamic instability, bacteremia, coagulopathy, prosthetic tricuspid valve, intra-atrial or venous thrombosis, and pregnancy.

A review of the testing of the QDOT MICRO™ catheter verifies that risks associated with the designs are acceptable and not unacceptable (Intolerable) risks have been noted. Any testing deviations are

discussed within the body of the respective testing reports and all deviations were reviewed and considered to be acceptable.

The designs of the QDOT MICRO™ catheter have been subjected to testing (bench top, thigh preparation, simulated clinical conditions via in vivo beating heart testing and EMC/Electrical Safety testing). The results of the various testing performed have verified the safety of the catheter when used in accordance with the Instructions for Use.

Biocompatibility and Sterility Assessments for the applicable catheter have been performed and verify that the proposed design and packaging meet the existing requirements for both categories.

A review of the risk assessment documents for the QDOT MICRO™ catheter have verified that there are no "Intolerable" ratings related to risks associated with the designs of the catheter. All ratings are "As Low As Practical" (ALAP).

### 1.3.2. Minimisation of Risk

Although there are potential risks posed during a cardiac RF ablation procedure, the criteria for subject selection, methods, personnel, facilities, and training that have been specified for this study are intended to minimize the risk to subjects undergoing this procedure.

Robust testing of the investigational devices at component and the system level, within simulated clinical conditions, was successful with no adverse events identified. During the QMODE+ design phase, systematic proactive risk analyses did not identify new hazards and harms. Minimization of Risk has been described per QDOT MICRO™ catheter IFUs within the section Warnings and Precautions for the QDOT MICRO™ Uni-Directional Catheter (M-5276-1043A), which are the same as those listed in the QDOT MICRO™ Bi-Directional IFU (M-5276-1042A) with the exception of the product name. The list of warnings and precautions entail pre-procedural and procedural precautions whereas postprocedural management is in accordance with the ACC/AHA/HRS 2017 Guidelines for the Management of Patients with Atrial Fibrillation. Additionally, the risk of potential adverse events is mitigated by the temperature cutoff setting of the generator and the optimization of the target temperature.

**Patient selection**: Subjects will be screened carefully prior to enrollment in the study to ensure compliance with the inclusion and exclusion criteria. Both criteria have been developed to reflect the population indicated for commercial use of the QDOT MICRO™ catheter. The exclusion criteria and contraindications have been developed to exclude subjects with a medical history or condition that relates to the contraindications per catheter IFUs and therefore their risk of (unanticipated) adverse events (refer to Section 4.2 for the Exclusion Criteria and the catheter IFUs).

**Procedure safeguard and post-procedural management:**
Investigators skilled in intracardiac mapping and ablation of AF with the use of RF ablation catheters containing contact force technology and qualified training experience with the use of the QDOT MICRO™ system will be selected for participation in the study. AF ablation procedures will be performed in electrophysiology laboratories with the assistance of skilled nurses and technicians. The laboratory will contain sufficient resuscitative equipment and facilities to manage any potential complications. Immediate access to cardiac surgical facilities, as well as a qualified cardiovascular surgeon, will be available during the ablation procedure in the event that surgical intervention becomes necessary.

To proactively manage serious and potentially life-threatening complications during an AF ablation procedure (Atrio-Esophageal Fistula, PV stenosis, Phrenic nerve paralysis and cerebral embolism), the following precautions are highly recommended:

- When ablating near the esophagus (along the posterior wall of the left atrium), take precautions to avoid injuring the esophagus. These may include beginning the ablation with reduced RF power, reducing contact force, reducing application time, increasing the time interval between ablations, esophageal visualization, and/or intraluminal esophageal temperature monitoring.
- When ablating near the phrenic nerve, take precautions to avoid injuring the phrenic nerve, including appropriately reducing RF power, and performing pacing maneuvers to identify the proximity of ablation electrode(s) to the nerve.
- To prevent stenosis of the pulmonary veins, do not place the catheter in the pulmonary veins during the application of RF energy.
- Inspect the saline within the irrigation tubing for air bubbles prior to its use in the procedure. Air bubbles in the irrigation saline may cause emboli.
- To prevent thromboembolism, intravenous heparin (target ACT of ≥325 s) should be administered prior to or immediately following transseptal puncture during AF ablation procedures. The 2017 HRS/EHRA/ECAS/ AOHRS/SOLAECCE expert consensus statement on catheter and surgical ablation of atrial fibrillation recommends systemic anticoagulation with warfarin or a direct thrombin or factor Xa inhibitor for at least 2 months following an AF ablation procedure.

Safety data during enrollment and short follow-up will be routinely monitored by the Medical Safety group.

### 1.3.3. Known Potential Benefits

Current practice guidelines reflect extensive expert reviews of published risks and benefits among various treatment modalities and patient populations. All key published guidelines agree that the primary clinical benefit of catheter ablation for PAF is an improvement in quality of life, following abatement of arrhythmia-related symptoms.

The role of catheter ablation as first-line therapy, prior to a trial of a Class I or III antiarrhythmic agent, has been suggested as an appropriate indication for catheter ablation of AF in patients with symptomatic paroxysmal or persistent AF by the HRS/EHRA/ECAS 2017 Consensus Statement [2]. In this circumstance, the benefits of catheter ablation outweigh the risks (Class IIa); however, the strength of evidence/data supporting this therapeutic modality (Level B) reflects a limited number of clinical studies. Not all expert bodies are in line with the aforementioned expert opinion.

The 2016 ESC-published guidelines and recommendations for the management of AF suggested that in patients who experience symptomatic recurrences of AF despite antiarrhythmic drug therapy, catheter ablation shows better sinus rhythm maintenance with catheter ablation than on antiarrhythmic drugs [49]. However, the guidelines also present that randomized trials showed only modestly improved rhythm outcome with catheter ablation compared to antiarrhythmic drug therapy [49].

Catheter ablation has been used for over two decades to treat AF patients to achieve PVI. Significant catheter design improvements (e.g., irrigated encircling catheters) focus upon improving physicians' abilities to achieve finite entrance block following PVI, reducing damage to neighboring structures and improving procedural efficiency.

The QDOT MICRO™ catheter is a steerable multi-electrode luminal catheter with a deflectable tip designed to facilitate electrophysiological mapping of the heart and to transmit radiofrequency (RF) current to the catheter tip electrode for ablation purposes. In addition to force-sensing technology, the catheter incorporates six thermocouple temperature sensors and three micro electrodes embedded in the 3.5 mm tip electrode.

The measured temperature can be used by the operator to assess the efficiency of ablation in real time. The localized temperature measurement will provide a highly sensitive measure of catheter location stability and/or movement during RF application and may reduce the need for additional RF applications.

The micro electrodes will provide high quality localized electrograms that will allow finer endocardial electrical mapping and a better assessment of possible conduction gaps in the ablation lesion sets used to isolate the pulmonary veins and determining bidirectional block of linear lesion sets.

Finally, the catheter tip has incorporated a new angled design of the irrigation ports. This new design allows for reduced incidence/risk of charring and coagulum on the catheter increasing safety during the ablation procedure.

With contact force information and improved temperature feedback in any tip tissue orientation, the QDOT MICRO™ catheter is designed to create durable lesions, in shorter time, with fewer ablation applications, and improved irrigation flow decreasing the opportunity for char and coagulum formation.

The expected benefits of the QDOT MICRO™ System, consisting of a radiofrequency ablation catheter combining microelectrodes, thermocouples, porous tip irrigation and contact force sensing with the nGEN Generator with QMODE+ modality software installed may improve safety and efficiency. There are several types of clinical benefits for catheter ablation that are not specific to the subject device. These catheter ablation clinical benefits include impact of the procedure on clinical management, patient health, and patient satisfaction in the target population.

The QDOT-MICRO™ System may potentially impact the procedure by the following:

- Limit conductive heating and collateral damage to neighboring structures including non-cardiac adjacent tissues.
- Increase catheter stability and reduce tissue edema, therefore improve lesion to lesion consistency at very high power for a short duration, since catheter instability in a constantly beating heart and tissue edema remains problematic for the effective lesions using the conventional ablation techniques.
- Contact force sensing capabilities and improved temperature feedback may aid in increasing the effectiveness of RF ablations by maintaining better control for a more effective lesion formation.
- Reduce the procedural time related to ablating the pulmonary vein triggers in the left atrium and improve the PVI efficiency significantly.
- Reduce fluoroscopy exposure for both the patient and the staff.
- Microelectrodes may aid in better assessment of possible conduction gaps in the ablation lesion sets.

- Reduce the amount of fluid loading of the patient as compared to a focal ablation catheter.

# 2. Objectives

The objective of this study is to evaluate the workflow and acute performance of the QDOT MICRO™ catheter used in combination with the nGEN Generator with QDOT software module for the treatment of Patients with Atrial Fibrillation during standard electrophysiology mapping and RF ablation procedures. In this study, QMODE+ will be used as the primary mode for pulmonary vein isolation. If the investigator deems QMODE+ is unable to achieve PVI, the study catheter in QMODE will be used to complete the procedure.

# 3. Study Design and Endpoints

## 3.1. Description of the Study Design

The QDOT-nGEN study is a prospective, multi-center, non-randomized, interventional clinical workflow study. The study population will consist of up to 50 subjects with minimum of 30 subjects who are scheduled to undergo a clinically indicated ablation procedure for the management of their AF. The study will be conducted at up to 6 centers in Canada.

## 3.2. Study Endpoints

### 3.2.1. Primary Endpoint(s)

The primary endpoint is to confirm pulmonary vein isolation. This is defined as confirmation of entrance block in all targeted PVs after adenosine and/or isoproterenol challenge using the nGEN/ QDOT Micro Ablation System.

### 3.2.2. Additional Endpoints

The following additional data will be collected and analyzed as part of this study. These data will include but not limited to:

- Adverse events will be collected and evaluated. All events will be reported to the Complaint Handling Unit (CHU).
- Procedural data associated with
  - Catheter ablations outside the PV area
  - PVI achieved with QMODE+ only among all targeted veins and by subject
  - PVI achieved with combined use of QMODE+ and QMODE among all targeted veins and by subject
  - Need for ablation of acute PV reconnection (touch-up) among all targeted veins and by subject
- Procedural parameters
  - Total procedure time
  - Mapping time
  - PV ablation time
  - Total ablation time
  - RF application time
  - Total Fluoroscopy time
- Total number of RF applications, % QMODE+ applications and % QMODE applications

- Anatomical location of touch-up applications using the QDOT catheter
- Temperature, power, contact force, impedance during RF application
- Confirmation of RF energy delivery from nGEN log files

# 4. Study Population

## 4.1. Participant Inclusion Criteria

Subjects must meet ALL the following inclusion criteria to be eligible for participation in this study:

1. Subjects diagnosed with symptomatic Paroxysmal or Early Persistent* AF undergoing a catheter ablation procedure through pulmonary vein isolation.
2. Age 18 or older.
3. Signed the Patient Informed Consent Form (ICF).

*Definitions for paroxysmal and early persistent AF are based on the 2017 HRS consensus statement.

## 4.2. Participant Exclusion Criteria

Subjects who meet ANY of the following exclusion criteria are not eligible for enrollment.

1. If the patient has had a ventriculotomy or atriotomy within the preceding twelve weeks.
2. Presence of a myxoma or an intracardiac thrombus.
3. Presence of prosthetic valves.
4. Presence of active systemic infection
5. Patient with an interatrial baffle or patch
6. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of child bearing age and plan on becoming pregnant during the course of the clinical investigation.

## 4.3. Contraindications

The following contraindications are referenced in the IFU for study

- If the patient has had a ventriculotomy or atriotomy within the preceding twelve weeks because the recent surgery may increase the risk of perforation.
- In patients with a myxoma or an intracardiac thrombus as the catheter could precipitate an embolus.
- In patients with prosthetic valves as the catheter may damage the prosthesis.
- In the coronary arterial vasculature due to risk of damage to the coronary arterial vasculature.
- In patients with an active systemic infection because this may increase the risk of cardiac infection.
- Via the transseptal approach in a patient with an interatrial baffle or patch because the opening could persist and produce an iatrogenic atrial shunt.
- Via the retrograde trans-aortic approach in patients who have had aortic valve replacement.
- With a long sheath or short introducer < 8.5 F in order to avoid damage to the catheter shaft.

## 4.4. Participant Withdrawal or Termination

### 4.4.1. Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request without penalty or loss of benefits to which they may otherwise be entitled. Participants will be informed prior to study entry that they are free to withdraw from the study at any time and for any reason without prejudice to their future medical care by a physician or the institution.

An investigator may terminate a subject's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Withdrawal is in the subjects' best interest
- The participant no longer meets eligibility criteria or meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Subject withdraws consent
- Subject is lost to follow up

Every subject should be encouraged to remain in the study until they have completed the protocol required 7-day follow-up period.

### 4.4.2. Handling of Participant Withdrawals or Termination

If a subject is removed or withdraws from the study, the date and reason for withdrawal will be recorded on the appropriate electronic case report form (eCRF). If the subject is withdrawn due to an adverse event (AE) or serious adverse event (SAE), the Investigator will follow the subject until the AE/SAE has resolved or is considered stable. The local CHU will collect the resolution information of any reported SAEs.

If a subject is unable to return for an office/clinic visit or cannot be contacted by telephone, 3 separate telephone calls should be made to obtain subject related safety information. All attempts should be documented in the source documents. If the subject does not respond to the 3 telephone calls, then the investigator must send a certified letter to the subject. If the subject does not respond to the letter, then the subject will be considered "lost to follow-up" for the study.

Subjects who have signed the ICF but are later found not to be eligible PRIOR to insertion of the study catheter will be excluded and might not count for the enrollment goal. Excluded subjects can be replaced with new enrolled subjects for the study to reach a total of the predefined evaluable study-subjects (up to 50).

## 4.5. Subject Enrollment Disposition

The following subject groups are defined:

- **Enrolled Subjects:** Patients who sign the informed consent form.
- **Excluded Subjects:** Subjects who are enrolled but never undergo insertion of the study catheter.
- **Discontinued Subjects**: Enrolled subjects who have the study catheter inserted but do not undergo ablation (no RF energy is delivered with the study catheter and the nGEN generator).

- **Lost to Follow-up Subjects:** Subjects for whom contact is lost after most recent visit (despite 3 documented attempts to contact the subject).
- **Withdrawn / Early Termination Subjects:** Subjects who withdraw consent for study participation or are withdrawn by the investigator, are terminated from the study prior to completion of all follow-up visits.
- **Completed Subjects:** Enrolled subjects who have not been excluded, discontinued, expired, withdrawn, terminated early, or lost-to-follow-up from the study prior to the final study visit.

# 5. Responsibilities

## 5.1. Investigator Responsibilities

Investigators at each participating clinical site will have the following responsibilities:

- Assuring compliance by site personnel with the provisions of the protocol
- Providing the Sponsor with:
    - Signed, dated Investigator Agreement
    - Written EC approval letters and EC-approved consent forms
    - Signed, dated Financial Disclosure form for each participating investigator
    - Curriculum vitae for each investigator
- Maintain an accurate and current Delegation of Authority log which identifies individuals authorized to perform work for the study and assuring compliance by site personnel with the provisions of the protocol
- Completing the appropriate training on the device (ablating investigators only) and the study protocol prior to enrolling and treating subjects
- Maintain accurate and current logs for the study such as:
    - Subject log, Device Accountability Log
- Obtain initial and amendment (if applicable) HC approval and annual review/approval thereafter for the study protocol and informed consent as applicable
- Obtain informed consent form and enroll patients
- Perform medical procedures
- Order tests required by the study protocol
- Review pre-procedure imaging pertaining to the pulmonary vein size prior to treatment
- Follow subjects until the end of the study protocol
- Accurately complete and sign eCRFs in a timely manner
- Maintain relevant source documentation and allow Sponsor direct access to perform monitoring or auditing duties
- Maintain records and provide reports according to prevailing regulatory requirements
- Share relevant study-related information with delegated study staff
- Inform the appropriate entities (e.g., Sponsor, HC) in a timely manner regarding the occurrence of AEs and/or product malfunctions.
- Making sufficient effort to maintain contact with treated subjects who fail to comply

with the follow-up requirements

- Maintain study records for at least 5 years or as specified per country specific record retention requirements after the study is completed and or terminated. The Sponsor will notify the Investigator of either of these events.
- Complying with HC and Sponsor annual report requirements, including the final report.

## 5.2. Sponsor Responsibilities

The Sponsor (Biosense Webster, Inc.) will be responsible for the following:

- Conduct of pre-study site assessment and approval.
- Preparation and modification (if applicable) of study documents including but not limited to the protocol, CRFs and informed consent
- Selection of appropriately qualified and trained individuals, including monitors, to conduct the study
- Conduct protocol and device training for investigators and research personnel as applicable
- Set-up of study-specific committees
- Obtain signed study contracts from investigators/hospitals, CROs and other involved parties
- Ship study devices to each site
- Monitor sites for the duration of the study
- Maintain study database
- Inform investigator of his/her responsibilities
- Submit and obtain approval for study from applicable regulatory agencies
- Preparation of reports summarizing the status of the study no less than annually. These reports will be supplied to the Principal Investigator at each site.
- Update Report of Priors, IFU, IB, and Risk Analyses, as applicable
- Update investigators on safety issues, if needed
- Report to study investigators and regulatory agencies, as required
- Have AEs reviewed by the study-specific committees, as required
- Communications with the competent authority
- Submission of any amendments to the Clinical Study Protocol/Post market clinical follow up plan to the competent authority.

# 6. Study Device Description

## 6.1. Device Acquisition

After obtaining a fully executed clinical trial agreement and appropriate HC approvals, the sponsor will initiate shipment(s) of the investigational device to the site. The Sponsor will keep records of all investigational devices shipped to the site. Approved investigational devices will be shipped directly to the site and will be received by the site. Investigators are responsible for appropriate logging of

the devices received, verification of packing slip information (i.e., lot numbers and quantity shipped), date and identity that each device was used in the study, disposition information regarding disposal or return to the Sponsor.

## 6.2. Device Storage and Stability

Devices are to be stored in accordance with the IFUs and User Manual. Do not use this device after the “Use By” date.

## 6.3. Device Preparation

Information related to device preparation can be found in the IFUs.

## 6.4. Instructions for Use

A comprehensive set of IFU/User manuals for the QDOT MICRO™ System, and all accessory cables/interface cables is contained in each product package and is also available upon request.

## 6.5. Device Description

### 6.5.1. QDOT MICRO™ Catheter

The Biosense Webster QDOT MICRO™ Navigation Catheter (Uni-Directional and Bi-Directional) and related accessory devices are indicated for catheter-based cardiac electrophysiological mapping (stimulating and recording) and, when used in conjunction with a compatible radiofrequency generator (including the nGEN Generator, D-1384-01), for cardiac ablation. The Biosense Webster QDOT MICRO™ Uni-Directional and Bi-Directional Navigation Catheter provides a real-time measurement of temperature and contact force between the catheter tip and heart wall, as well as location information when used with the CARTO™ 3 System.

The catheter has a high-torque shaft with deflectable tip section containing an array of electrodes which includes a 3.5 mm tip dome with three microelectrodes. All of the electrodes may be used for recording and stimulation purposes. The tip electrode serves to deliver RF energy from the RF generator to the desired ablation site. The tip electrode and ring electrodes are made from noble metals.

The catheter incorporates six thermocouple temperature sensors that are embedded in the 3.5 mm tip electrode.

At the proximal end of the catheter, a saline input port with a standard Luer fitting terminates from the open lumen. This saline port serves to permit the injection of normal saline to irrigate the tip electrode. During ablation, heparinized normal saline is passed through the internal lumen of the catheter and through the tip electrode, to irrigate and cool the ablation site as well as the electrode tip. An irrigation pump should be used to control the saline irrigation.

**Figure 1. Overview of the QDOT MICRO™ Catheter with Uni-directional and Bi-directional Tip Deflection**

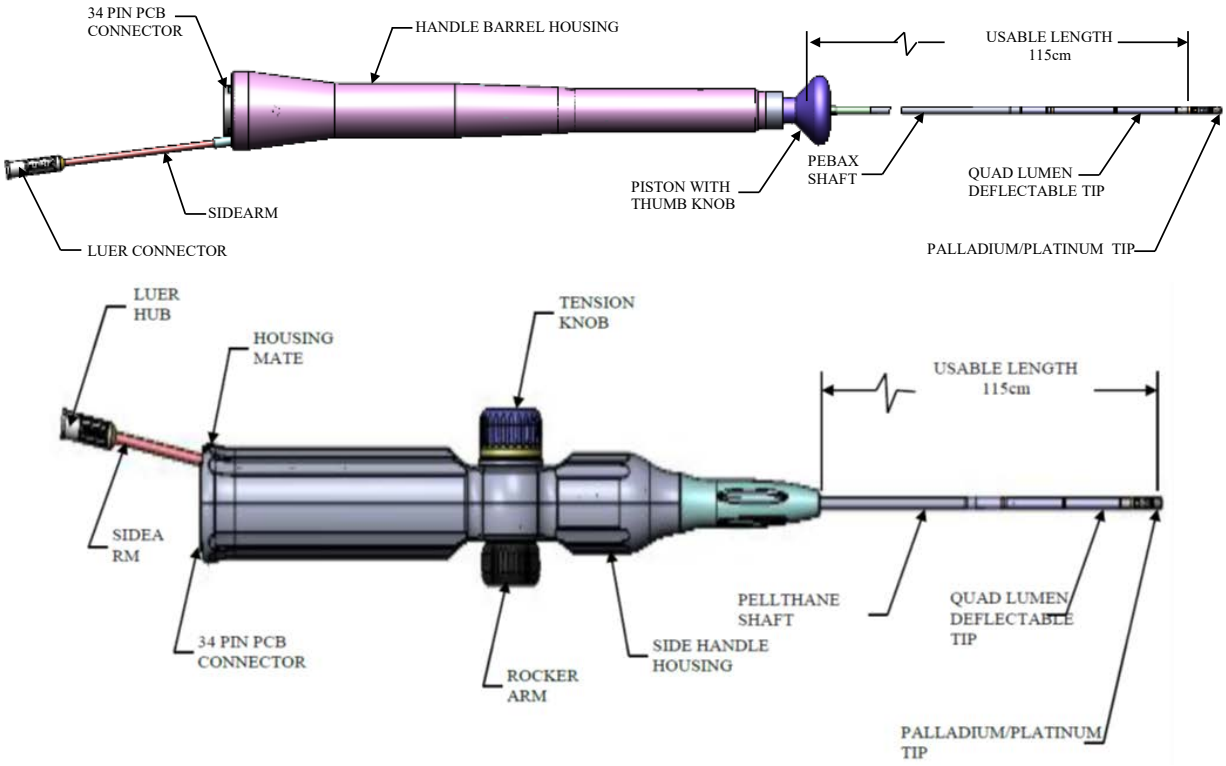
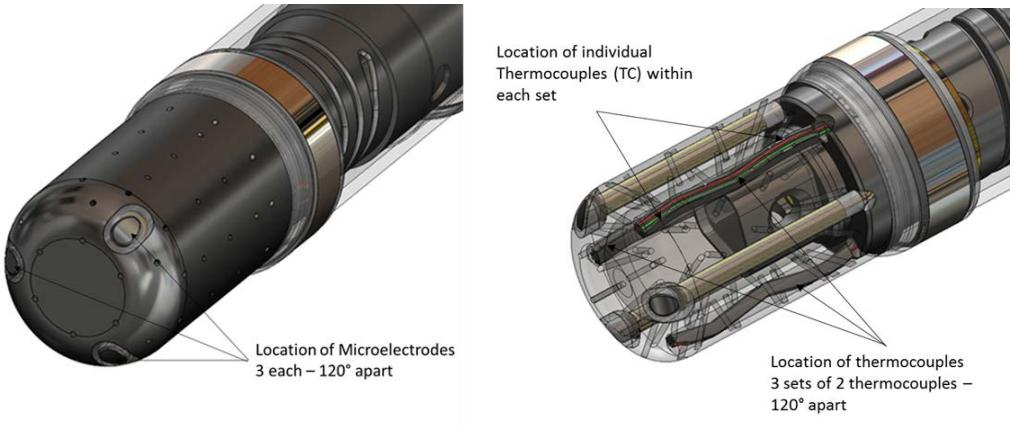



**Figure 2. QDOT MICRO™ tip Section**

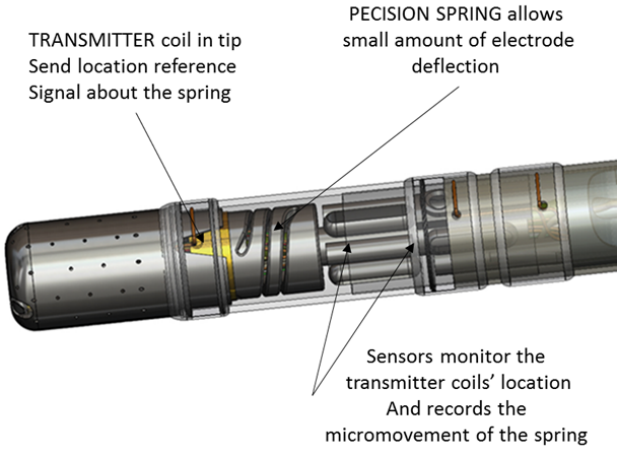
**Figure 3. QDOT MICRO™ tip with Thermocouples (6), µElectrodes (3) and angled irrigation ports**




An irrigation pump is used to control the saline irrigation. The catheter interfaces with standard recording equipment and a compatible RF generator via accessory extension cables with the appropriate connectors.

This catheter features a location sensor embedded in the tip section that transmits location and contact force information to the CARTO® 3 (Version 6.0 or above) Navigation System (refer to Figure 4). An appropriate reference device is required for location reference position purposes. For information on using the catheter in mapping procedures and for information on appropriate reference devices, refer to the user manual for the CARTO® 3 (Version 6.0 or above) Navigation System.

**Figure 4. Contact Force Sensor – External View**




This catheter features a location sensor embedded in the tip section that transmits location and contact force information to the CARTO® 3 System. An appropriate reference device is required for location reference position purposes. The catheter connects to the CARTO® 3 Navigation System through an interface box called the Patient Interface Unit (PIU). The catheter interfaces with standard recording equipment and a compatible RF generator via accessory extension cables with the appropriate connectors. For use in mapping procedures, for information on appropriate

reference devices, and for further description of the operation of the CARTO® 3 Navigation System, refer to the CARTO® 3 Navigation System User Manual.

For further information on the irrigation pump (nGEN® Pump), RF Generator (nGEN Generator), and required cables, refer to the respective Instructions for Use and/or User Manual.

Refer to Section 6.6 (Required Study Equipment) for details on additional equipment required for this study.

### 6.5.2. Bi-directional Catheter Description (D-1395-XX-S)

The catheter has a high-torque shaft with a bi-directional deflectable tip section containing an array of electrodes which includes a 3.5 mm tip dome. All of the electrodes may be used for recording and stimulation purposes. The tip electrode serves to deliver RF energy from the generator to the desired ablation site. The tip electrode and ring electrodes are made from noble metals. The catheter incorporates six thermocouple temperature sensors and ECG electrodes that are embedded in the 3.5 mm tip electrode. A Rocker Lever is used to deflect the tip. The high-torque shaft also allows the plane of the curved tip to be rotated to facilitate accurate positioning of the catheter tip at the desired site. Additionally, a variety of curve types are available in symmetric or asymmetric combinations, providing two 180° opposed, single-planed curves. Five curve configurations designated “DD”, “FF”, “JJ”, “DF”, and “FJ” are available.

### 6.5.3. Uni-directional Catheter Description (D-1394-XX-S)

The catheter has a high-torque shaft with a uni-directional deflectable tip section containing an array of electrodes which includes a 3.5 mm tip dome. All of the electrodes may be used for recording and stimulation purposes. The tip electrode serves to deliver RF energy current from the generator to the desired ablation site. The tip electrode and ring electrodes are made from noble metals. The catheter incorporates six thermocouple temperature sensors and ECG electrodes that are embedded in the 3.5 mm tip electrode. A Rocker Lever is used to deflect the tip. The high-torque shaft also allows the plane of the curved tip to be rotated to facilitate accurate positioning of the catheter tip at the desired site. Three curve types configurations designated “D,” “F,” and “J” are available.

### 6.5.4. nGEN Generator (D-1384-01)

The nGEN™ Generator is indicated for use in cardiac ablation. The generator is a highly specialized device used in conjunction with compatible cardiac ablation catheters and a dispersive pad (indifferent electrode) to create a closed electrical circuit capable of delivering specified doses of RF energy. The RF energy is delivered to cardiac tissue that forms unwanted electrical pathways that either drive or maintain arrhythmias. The RF energy heats the tissue so that it becomes denatured and no longer functional. This interrupts and/or destroys the unwanted electrical pathways, thereby restoring normal heart function.

The nGEN Generator actively generates RF energy and continuously monitors, displays, and coordinates the amount of RF energy delivered, the temperature of the catheter’s ablation electrode(s), and the tissue impedance during ablation. Simultaneously, an impedance measurement mechanism measures the heart tissue impedance allowing detection of small tissue changes before, during, and after treatment. Before and during treatment, electrical signals generated by the heart are also detected and transmitted by the catheter through the generator to the connected CARTO® 3 System and monitoring instruments.

The nGEN™ Generator consists of the following components:

- Monitor: The monitor is a touch screen computer that contains the software. The monitor has a control knob and physical start and stop buttons. The monitor is supplied with a base which can be detached. An optional second monitor may also be used.
- The monitor software includes a base software, which consists of all basic GUI screens required for the operation of the monitor software, and the configuration files, which are installed based on the catheter presets.
- Console: The console produces and controls the delivery of RF energy. The console also connects to and communicates with therapeutic catheters and other devices.
- Power Supply Unit (PSU): The PSU provides power to the console.
- Pedal: The pedal is an alternate way to start and stop an ablation session.
- Cables: The nGEN™ Generator is shipped with cables for connecting the generator components to each other and to other devices.

Both the internal hardware and software design of the nGEN Generator incorporate a safety architecture that enables independent monitoring of critical parameters (e.g. RF time, power delivery, temperature, impedance). All safety-critical parameters, i.e. voltage and current measures, temperature measurements, and start/stop ablations, are implemented via two independent paths: a primary control path and a secondary safety monitoring path. Since the start and stop commands can be initiated from various sources, the paths may include both digital and analog communications. This two-path design is intended to prevent common cause events that may lead to safety hazard. The continuous crosschecks of critical parameters between the console software and the monitor software mitigate systemic failures and enhance safety.

When used with the irrigated catheters, the nGEN Generator is connected to the nGEN Pump by a communication interface that allows both the generator and the pump to be controlled from the touch screen on the monitor. The nGEN Pump is connected to the catheter irrigation port to provide irrigation during ablation for irrigated catheters.

The generator can be configured to support various BWI therapeutic ablation catheter families. This nGEN Generator version (console software version2.0.3 and above /monitor software version 2.0.0 and above) utilized in this clinical study is configured for use solely in combination with the QDOT MICRO Catheter in conventional intracardiac RF ablation procedures.

**Figure 5: nGEN Generator**

### 6.5.5. nGEN™ Pump (D-1397-01)

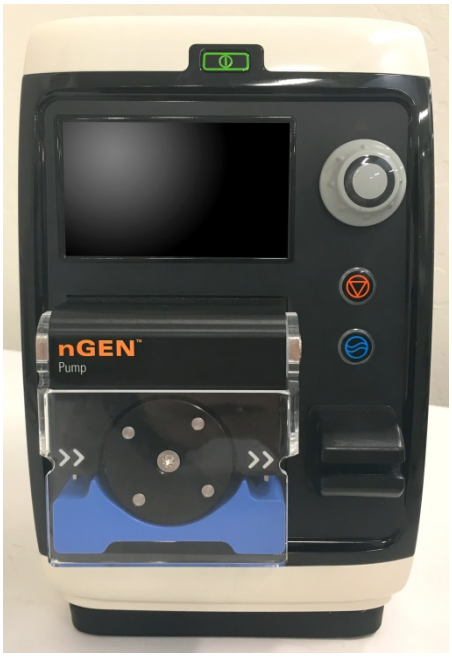
The nGEN™ Pump is a peristaltic pump designed for use by electrophysiology laboratory staff in cardiac electrophysiology procedures. The pump delivers irrigation solution from a connected irrigation solution bag via a compatible irrigation tubing set to a compatible irrigated catheter.

When the pump is connected to the nGEN Generator, the generator automatically sets the irrigation flow rate based on the connected catheter type, changes the flow rate when the delivery of RF energy starts and stops, and monitors the flow rate.

Only compatible accessories and devices provided by or recommended by Biosense Webster may be used with the nGEN™ Pump.

This nGEN pump is compatible with nGEN generator and SMARTABLATE™ Irrigation Tubing Set.

**Figure 6: nGEN pump**




### 6.5.6. TX eco EXT Interface Cable (D-1357-03-S)

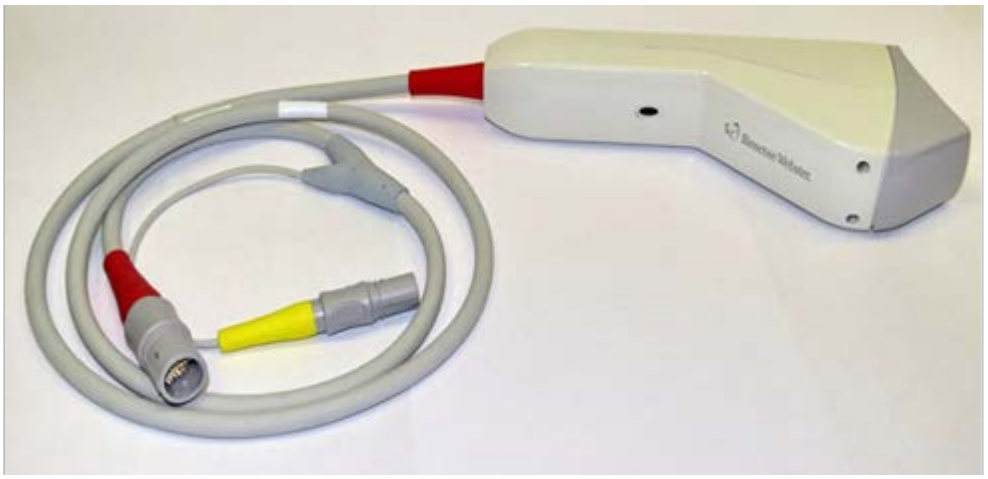
The TX eco EXT Connection Cable (D-1357-03-S) is designed to connect the QDOT MICRO™ Catheter that interfaces the Patient Interface Unit (PIU) of the CARTO® 3 EP Navigation System via the dongle. The TX eco EXT Connection Cable consists of a gray connector which connects to the dongle and a black connector that connects to the catheter receptacle.

**Figure 7: TX eco EXT Connection Cable**

### 6.5.7. TX eco Cable Dongle (D-1401-02)

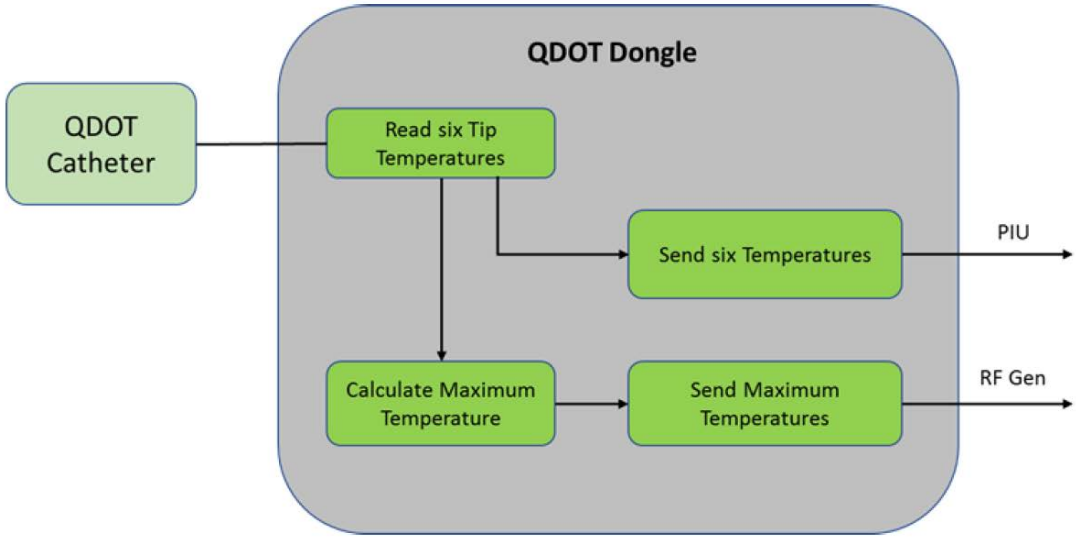
The Biosense Webster TX eco Cable (Dongle) (D-1401-02) is an accessory device primarily intended to provide a means for the QDOT MICRO™ Catheter to interface with the CARTO® 3 (Version 6.0 or above) EP Navigation System and to the nGEN generator. The TX eco Cable (Dongle) processes and transfers catheter location signals to the CARTO® 3 System. Additionally, the TX eco Cable (Dongle) contains integrated firmware that reads the temperature from each thermocouple (six total) within the QDOT MICRO™ Catheter tip. The highest temperature will be sent to the compatible RF Generator and all six temperatures will be sent to the CARTO®3 System for real-time visual display.

**Figure 8. TX eco Cable (Dongle) with Extension Cable**



Refer to Figure 9 below which depicts a functional block diagram of the TX eco Cable (Dongle) signal processing and transfer activities.

**Figure 9. Block Diagram of the TX eco Cable (Dongle) Processing and Transfer Activities**



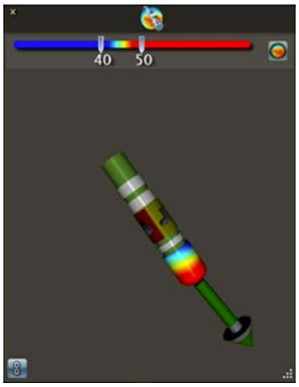

### 6.5.8. CARTO® 3 (Version 6.0 or above) QDOT MICRO™™ Software Module

The QDOT MICRO™ software module is a software feature to the CARTO® 3 System to display and record ECG, temperature, location and contact force information when the QDOT MICRO™ Catheter is connected and the QDOT MICRO™ software module is enabled. The temperatures recorded by the 6 thermocouples within the QDOT MICRO™ Catheter are transmitted to and displayed graphically on the CARTO® 3 System. The purpose of sending all six (6) temperature readings to the CARTO® 3 System is to provide two graphical displays to the physician on the CARTO® 3 System.

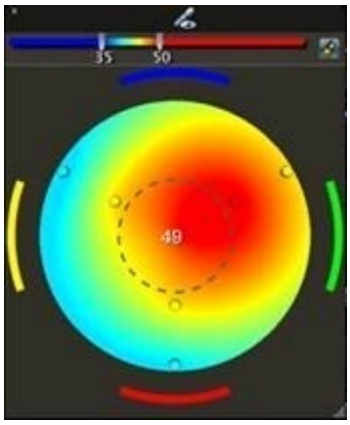
**Tip Temperature Display**

The CARTO® 3 System will display the temperature measured by the TX eco Cable in colored 2D and 3D imaging format. The image on the left is the temperature distribution around the tip electrode. The image on the right is the “bullseye” display.

**Figure 10. Information Displayed on the CARTO® 3 System**




**Colored catheter temperature distribution 3D display**



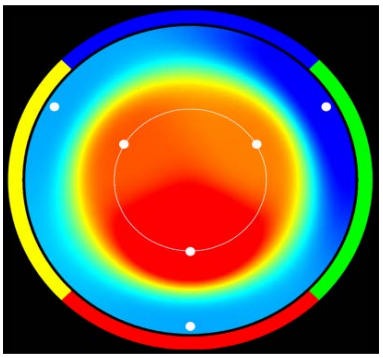

**"Bulls eye" 2D display of values for each thermocouple reading**

The "bulls eye" display provides temperature information to the physician. An optional numerical value of the temperature from the RF Generator is displayed on the "bulls eye" determined by the physician's preference to display or not to display). The colored graphic of the bulls eye provides relative tip to tissue interface temperature readings obtained from the 6 thermocouples. The colored tip graphic provides the physician with an indication as to which part of the catheter tip has contact with the tissue. In addition, it can also provide the physician with an indication of the catheter's tip to tissue stability; if the catheter tip slips, the temperatures obtained from the thermocouples will change which will be visually displayed on the "bulls eye" as well as on the graphic of the tip of the catheter. The colors in the displays change as the temperature of the thermocouples change. The colors range from dark blue (minimum temperature) to dark red (maximum temperature) and the circular presentation allows the physician to visualize the relative temperatures of distal and proximal thermocouples in the tip (viewed from the center outward). The outer halo provides the orientation of the catheter tip in 3-dimensional space.

The TX eco Cable is responsible for gathering the QDOT MICRO™ Catheter temperature and micro electrode signal information and transferring this data to the CARTO® 3 System for display. The temperature feedback display during ablation is described below.

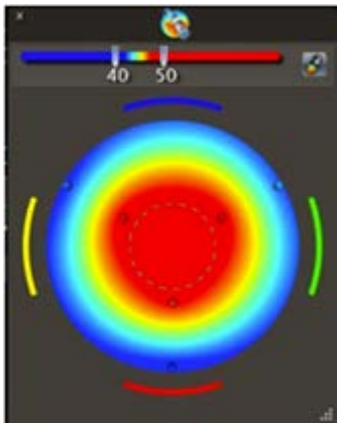
- Tip Temperature Distribution - monitor the maximum temperature measured and verify the proper response of the temperature distribution of the catheter tip during the RF session. In the figure below, the six small circles represent the 6 thermocouples: 3 distal and 3 proximal. The inner circle represents the tip electrode and the outer ring represents the tip sides.

**Figure 11. Temperature Distribution Display**



Any change in the desired Ablation catheter tip orientation – from a perpendicular orientation to the tissue, would result in temperature rise of the corresponding part of the catheter tip electrode, as indicated by the red color the tip temperature distribution display as shown below.

**Figure 12. Temperature Display for Perpendicular Catheter Tip Orientation**




- Any change in the desired Ablation catheter tip orientation – from a parallel orientation to the tissue, would result in maximum temperature rise of the cylindrical part of the tip that is in contact with the tissue. This is indicated by the red color at the tip temperature distribution display, as shown below.

**Figure 13. Temperature display for Parallel Catheter Tip Orientation**

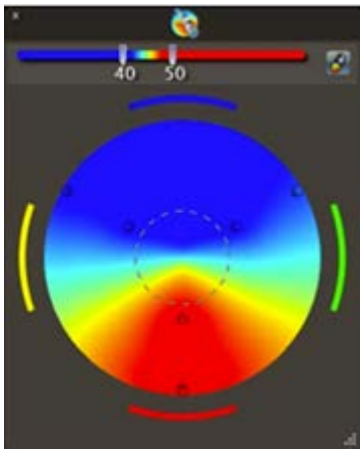
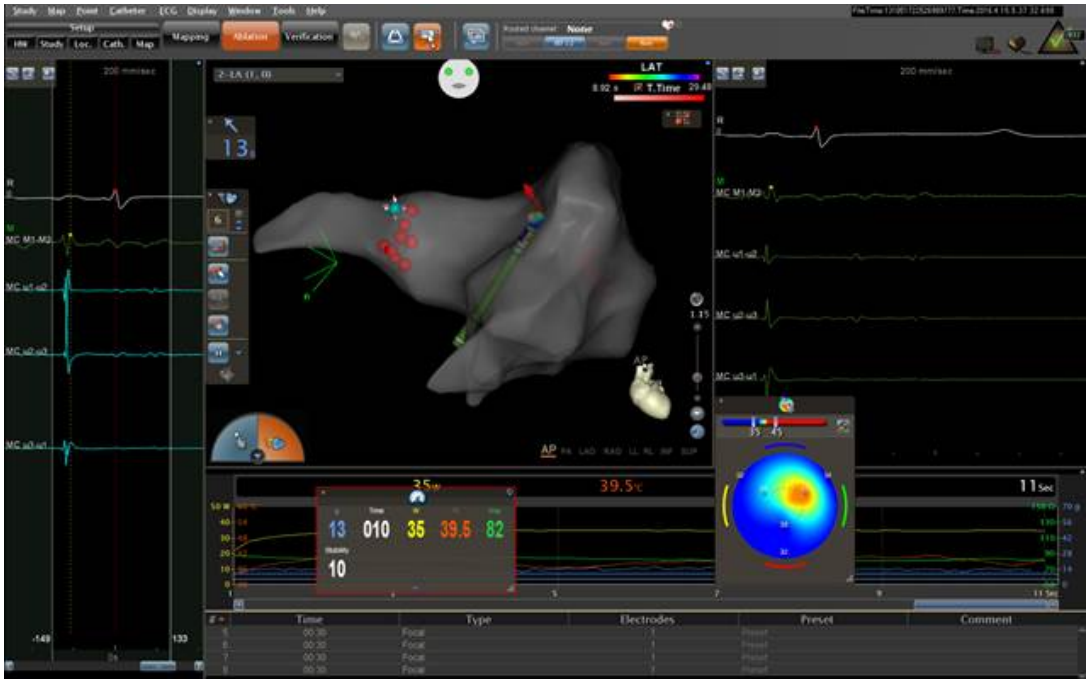



**Figure 14. CARTO® 3 GUI with RF generator in Unipolar Mode, QDOT MIDRO™ Catheter**




### 6.5.9. *Ablation Parameters for the QDOT MICRO™™ Catheter*

The ablation algorithm is designed to maximize RF lesion efficiency by using temperature feedback from the tip to adjust power and irrigation flow. The QMODE Temperature mode monitors the temperature rate of change in relationship to the set target temperature during RF application. To maintain desired power levels at a safe temperature, the QMODE adjusts the irrigation flow rate as a first order of control. A secondary control of power titration is also used if the temperature cannot be maintained with the increased irrigation flow rate alone. Typical temperature control algorithms for mainstream commercial irrigation RF catheters rely purely on power titration to maintain the desired temperature. By utilizing the irrigation flow rate first, the Q-dot catheter is able to deliver consistent power for efficient ablations without compromise of safety.

**RF Energy Modulation:**

The RF energy application is separated into two distinct zones: 1-50W and 90W.

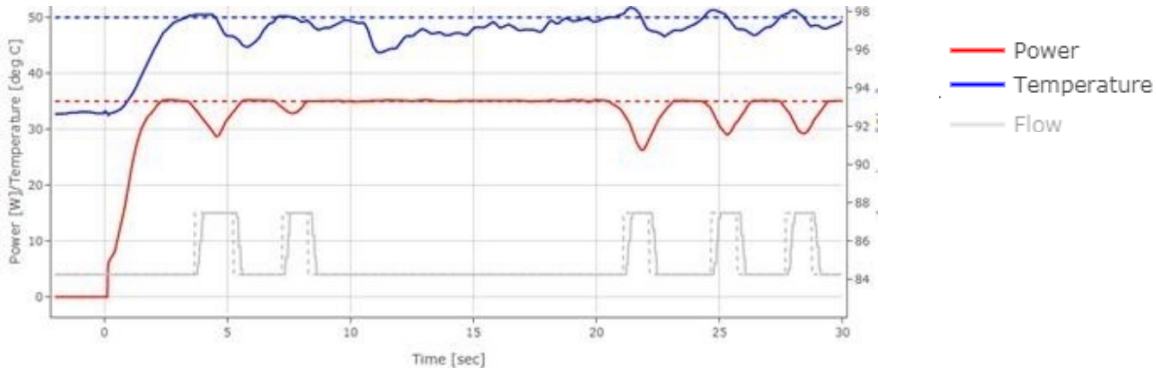
For power settings from 1-50W, the approach is to modulate irrigation and then titrate power as needed to maintain the target temperature. As an example (see Figure 15A), the power delivery (e.g. 35W) would start with the irrigation setting at 4 ml/min until it reaches a target temperature (e.g. 50°C). When the catheter reaches the target temperature, irrigation is then changed to 15 ml/min automatically by the generator algorithm. This increase in irrigation flow rate cools the tip and allows the generator to maintain the delivered power. If the temperature decreases, the pump irrigation flow rate is returned to the lower setting (i.e. 4mL). Under circumstances when increased irrigation flow does not sufficiently reduce the tip temperature, power delivery is automatically reduced.

In a second example (see Figure 15B), the power delivery (e.g. 50W) starts with the irrigation setting at 15 ml/min until it reaches a target temperature (e.g. 50°C). If the catheter is below the desired temperature initially, the irrigation is automatically reduced to 4ml/min by the generator algorithm to maximize the sensitivity to temperature. Once the temperature sensed at the tip starts to rise, the generator automatically increases the irrigation flow back to 15 ml/min. This cycle continues between low and high irrigation settings in order to maintain the target temperature. Again, under circumstances where the tip temperature is above 50°C, the power delivery is automatically reduced.

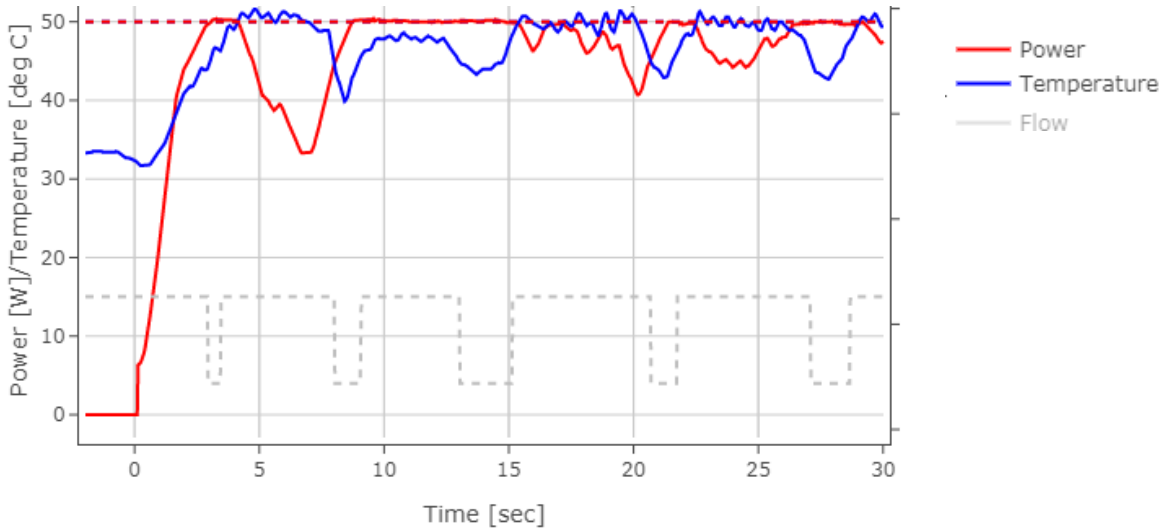
For power settings at 90W (Figures 15C and 15D), the maximum duration is 4 seconds. Therefore, the approach is to only titrate power. At this setting, power delivery is delivered at a constant irrigation flow of 8 ml/min with no modulation given the short duration.

## Figure 15A-D: Graphs of the Generator Power over Time

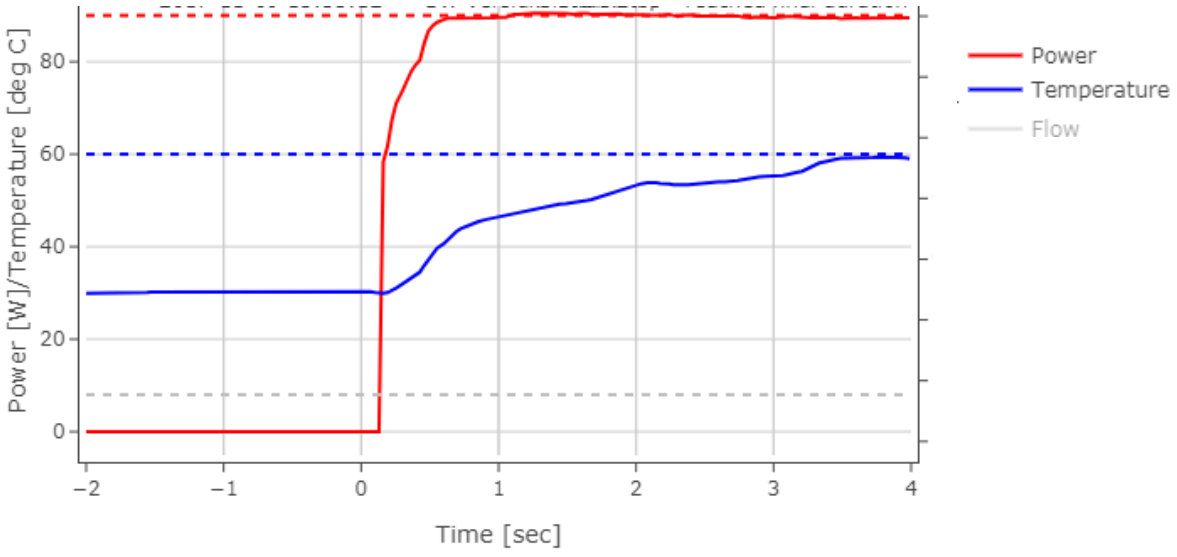
### A. RF Power Delivery at 35W



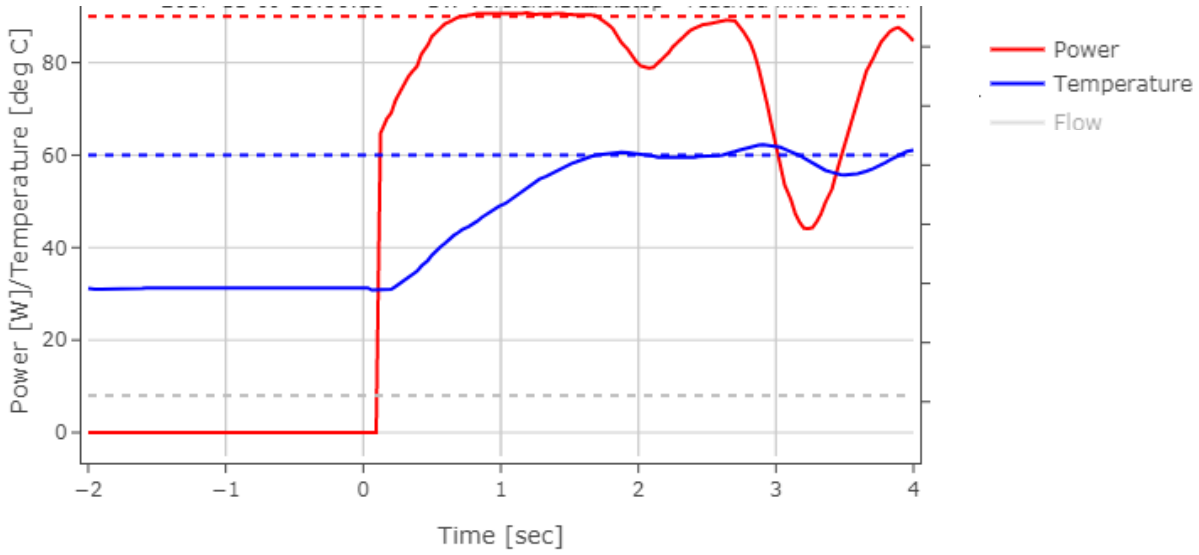

### B. RF Power Delivery at 50W




### C.RF Power Delivery at 90W



**D. RF Power Delivery at 90W, power titration evident**




## 6.6. Equipment

## 6.7. System Components and Setup

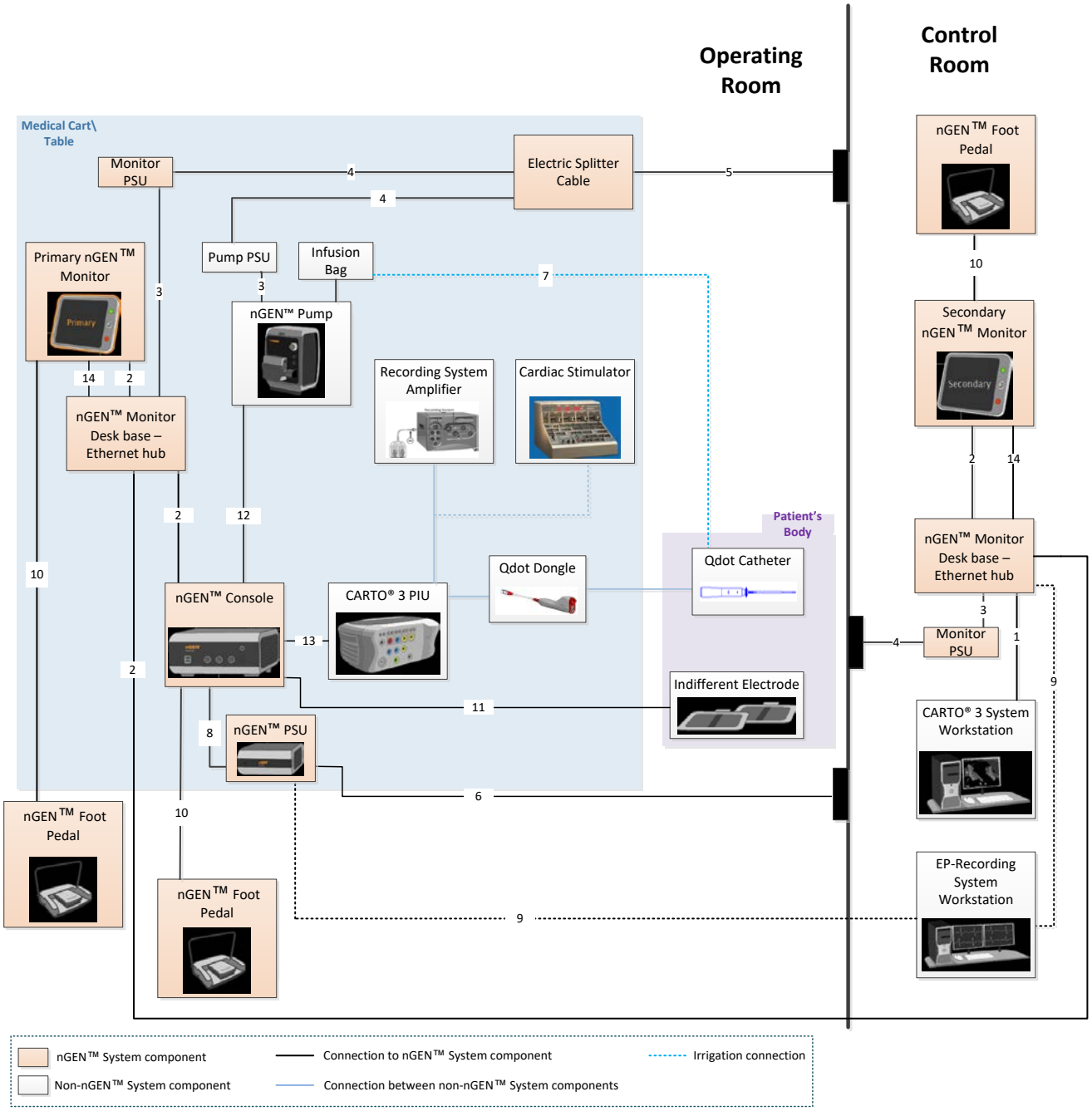
Some devices and software used in this study are investigational and some are available commercially at the hospital. Table below shows the investigational and non-investigational equipment used in the study.

**Table 2. Standard equipment used for this study**

| Equipment | Function or Specifics |
|---|---|
| **Investigational Equipment** | |
| **nGEN Generator (D-1384-01)** | **Transmits RF energy to the Ablation Catheter** |
| **Non-Investigational Equipment** | |
| **8.5 F compatible sheath** | **Facilitate deployment of catheter into the atria.** |
| **Lasso® or PentaRay® (optional)** | **Pre-ablation recording and mapping of the atria of the heart with the CARTO® 3 system.** |
| **SMARTABLATE™ Irrigation Tubing Set** | **Delivers heparinized saline to the catheter for cooling during the RF energy application** |
| **Esophageal temperature monitoring device** | **Esophageal temperature monitoring** |
| **EP lab recording equipment** | **Records multiple intracardiac electrograms and signals from the RF generator (power, temperature, impedance) and performs electrical stimulation.** |
| **Adhesive electrical dispersive pads / indifferent electrode** | **Component of the RF current return path (Valley Lab required)** |
| **Interface Cables** | **Connection of choice** |
| **CARTO® System Junction Box** | **Provide the interface to the catheter, generator, and the CARTO® System.** |
| **CARTO® 3 Version 6.0 or above** | **For mapping and visualization information.** |
| **nGEN Pump (Part Number D-1397-01)** | **Works with compatible irrigation tubing set to deliver irrigation solution to compatible irrigated catheters.** |
| **QDOT MICRO™™ Catheters D-1394-XX-S D-1395-XX-S** | **Delivers RF energy to the target tissue.** |
| **TX eco EXT Connection Cable (D-1357-03-S)** | **Provides a means to interface the QDOT MICRO™ catheters with the Dongle** |
| **TX eco Cable (Dongle) (D-1401-02)** | **Provides a means to interface the QDOT MICRO™ catheters to the Multi-Channel RF Generator** |

For RF ablation, the QDOT MICRO™ Catheter is connected to the CARTO 3 System Patient Interface Unit (PIU), which is connected to the RF generator. A Biosense Webster TX eco Cable (dongle) and compatible interface cable is required to achieve a proper generator interface. To complete the electrical circuit, an indifferent electrode must be connected to the indifferent electrode input on the generator. A schematic depiction of the QDOT MICRO Catheter system set up is provided in Figure 16.

**Figure 16. nGEN™ Generator System Connectivity Diagram**




# 7. Study Medication

For the purpose of this study, it is highly recommended to comply with the medication management as described per HRS consensus guidelines 2017.[2]

The following medications are recommended for subjects undergoing a study catheter ablation for AF.

- **Before the AF Ablation procedure**
  - Uninterrupted systemic anticoagulation therapy is recommended for at least 3 weeks prior to the AF ablation procedure.
    - If receiving warfarin/coumadin therapy, subjects must have an international

normalized ratio (INR) ≥ 2 for at least 3 weeks prior to treatment and the subject's must be confirmed to be ≥ 2 within 48 hours pre-procedure.

- **During the AF Ablation procedure**

  - Administer a heparin bolus PRIOR to transseptal puncture.
  - Target an ACT of at least ≥325 seconds, prior to or immediately following transseptal puncture and throughout the procedure.
  - It's strongly recommended to check ACT levels on regular basis during the procedure to ensure an ACT target of at least ≥325 seconds
  - Adenosine or isoprotenerol challenge is mandatory for the purposes of this study unless the subject is contraindicated for one of these medications.
    - Adenosine: A (12 to 24 mg) to confirm PV isolation; rule out dormant conduction
      **OR**
    - Isoproterenol to achieve a ≥20 beats per minute increase in heart rate to induce AF upon completion of the ablation procedure is recommended if pacing maneuvers are not performed (recommended dose range is 2-20 mcg/min).

- **Following the AF Ablation procedure**
  - Anticoagulation therapy is strongly recommended for at least 2 months following ablation.
  - Additional medications needed to treat clinical indications are at the discretion of the clinical investigation physician.
  - AAD management during the study will be at the discretion of the investigator

# 8. Study Schedule

## 8.1. Screening and Informed Consent

All patients considered for RF ablation procedure for drug refractory recurrent symptomatic AF should be evaluated by the investigator or designated member of the research team for study eligibility per the protocol inclusion and exclusion criteria.

The study investigator or designated member of the research team will obtain written informed consent from the subject. The patient informed consent procedure must be done within 60 days before the actual study procedure takes place. The background of the proposed study and the potential benefits and risks of the study should be explained to the subject. The subject must sign the consent form prior to any study-specific exams or tests are provided to them that fall outside of the standard of care. The consent form used must have prior approval from the regulatory authorities (as applicable) and study site's Ethics Committee. Failure to obtain informed consent renders the subject ineligible for participation in the study.

The investigator and/or designee must also clearly document the process of obtaining informed consent in the subject's source documents. The voluntary process of informed consent confirms the subject's willingness to participate in the study. It's the investigator's responsibility to ensure that the informed consent process is performed in accordance with ICH-GCP and with applicable local and federal regulations. If new information becomes available that can significantly affect a subject's future health and/or medical care, this information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing by dating and signing an amended ICF.

Each subject screened for enrollment in the clinical study who signs the patient informed consent form will be enrolled into the study. No subject should undergo any clinical investigation specific tests or examinations that fall outside the standard of care without first signing the patient informed consent form for this clinical investigation.

## 8.2. Baseline Evaluation and Procedures

### 8.2.1. Pre-Procedure/Baseline Assessments

Below pre-procedure assessments and data collection must be performed within 60 days prior to the ablation procedure

- **Patient Information and Consent**
- **Demographics** (age, gender, etc.).
- **Medical history,** including but not limited to arrhythmia, heart disease, thromboembolic events, lung/respiratory problems.
- **AF history** (first evidence of AF, number of episodes, symptoms, etc.).
- **Medication history**: Medication history (cardiac medication, AAD medication, anticoagulation regimen and any other clinically significant medication history) shall be gathered by interview or from medical records following enrolment but prior to the ablation procedure and should be recorded in the eCRF.
- **Cardiac medication and anticoagulation regimen:** Uninterrupted systemic anticoagulation therapy is recommended for at least 3 weeks prior to the AF ablation procedure.
- **Imaging for detection of LA thrombus:** performed within 48 hours prior of the study procedure or day of ablation procedure. The following are allowable imaging modalities:
  - TEE
  - CT/MRI
  - Intracardiac Echocardiography (ICE)
- **Pregnancy Test:** Pre-menopausal women only, performed within one week prior to the procedure.
- **Adverse Events** must be collected from the time the subject signs the informed consent onwards

### 8.2.2. Study Ablation Procedure Guidelines

#### 8.2.2.1 Recommended Ablation Parameters and irrigation pump settings

In this study protocol, QMODE+ is to be used as the primary mode for pulmonary vein isolation. Only after the investigator deems that QMODE+ is unable to achieve PVI should the study catheter in QMODE be used to complete the procedure.

**Table 3. RF and Flow Settings during RF applications**

| Power | Target Temp* | | Cut-off Temp | | Nominal Irrigation Flow rate |
|---|---|---|---|---|---|
| | Range | Maximum allowed | Range | Maximum allowed | |
| 25-35 W | 40-50ºC | 50ºC | 50-55ºC | 55ºC | 4mL** |
| 36-50W*** | 40-50ºC | 50ºC | 50-55ºC | 55ºC | 15mL** |
| 90W† | 40-60ºC | 60ºC | 60-70ºC | 70ºC | 8mL** |

* Temperatures displayed on the RF generator do not represent tissue temperature or electrode tissue interface temperature.
**A minimum flow rate of 2mL during mapping is recommended.
*** RF applications at 36-50W should not exceed 60 sec.
† The study recommends using this power setting for PVI as a primary ablation Strategy. RF applications at this power setting are limited up to 4 sec. It is recommended to use lower target temperature setting for the posterior wall RF applications.

Note: The QMODE and QMODE+ parameters, presented in Table A, are user-adjustable, in case the investigator deems appropriate.

#### 8.2.2.2 QDOT MICRO™ Contact Force (CF) Settings:

When using the study catheter in both QMODE and QMODE+, operators should Target:

- Target CF: 10g
- CF Range: 5-30g

#### 8.2.2.3 Recommended AF Ablation Procedure Sequence

Subjects will arrive to the electrophysiology laboratory for their ablation procedure and will undergo preparation for the procedure per the hospital's standard protocol (discretion of investigator).

*The AF ablation procedure workflow is recommended to follow the sequence below:*

- Anesthesia or sedation should be delivered per standard EP lab procedure.
- Placement of diagnostic catheters
- Cardioversion if subject not in sinus rhythm (per investigator discretion)
- CARTO® Respiratory Gating (unless using Jet Ventilation)
- Administration of heparin bolus prior to transseptal puncture or immediately following transseptal puncture
- Transseptal puncture
- Following successful transseptal puncture, an anatomic map can be performed, utilizing Lasso® or PentaRay® (or other at investigator discretion)
  Note: An anatomical map is not required for triggers outside the left atrium (e.g. SVC/CS etc.)
- Placement of esophageal temperature monitoring device (per investigator discretion)

- Confirmation of target ACT is ≥325 sec (but preferable 350 sec) prior or immediately after transseptal but no later than first ablation into the left atrium and maintain throughout the procedure
- Introduction of the QDOT MICRO™ catheter
    - Use the AUTOTAG feature in CARTO® 3 (Version 6.0 or above) to tag each QMODE+ ablation point after each application
    - At the new location ensure catheter stability before commencing RF application.
    - A pre-ablation flow rate delay of minimal 2 seconds will occur before RF application
    - Ablation modality: RF power application of up to 90W for up to 4 seconds (QMODE+)
    - Move the catheter to a new location (~4mm) if clinically effective ablation is achieved
    - QMODE+ should be used for full PV encirclement. If the investigator deems that QMODE+ is unable to achieve PVI, the study catheter in QMODE should be used to complete the procedure
    - Continue RF applications and catheter movement until the circumferential PVI is completed.
    - Precautions:
        - If the temperature increases above the temperature cutoff (default 65°C), RF application will stop immediately (automatically)
        - The decision to interrupt RF power delivery at any time during ablation should be guided by Clinical Investigator judgment and the monitoring of ablation effectiveness parameters commonly used such as EGM reduction and/or impedance changes.
- All subjects will continue PV ablation until PVI is achieved and isolation is confirmed by Lasso® or PentaRay® (or other at investigator discretion).
- After PVI is confirmed, it's recommended to initiate a 20-min waiting period
- Verify the ablation lines with a mapping catheter (Lasso® or PentaRay® or other at investigator discretion)
- Perform additional applications, if required
- Administer adenosine or isoproterenol for each targeted PV to rule out dormant conduction, mandatory unless subject is contraindicated for adenosine
- Perform additional applications (touch-up), if required
- Confirmation of entrance block of all targeted PVs

#### 8.2.2.4 Ablation Procedure Guidelines

General Introduction of the Study Catheter

When ablating near adjacent anatomical structures, take precautions to minimize collateral damage to the adjacent structures:

- When ablating near the esophagus (along the posterior wall of the left atrium), take precautions to avoid injuring the esophagus
- Prior to ablation in the region of the right superior PV, precautionary measures are recommended to evaluate proximity to the phrenic nerve, such as pacing maneuvers

Ablation outside the PV Ostia

The ablation procedure includes PVI, ablation of non-PV triggers and substrate modification. For RF application outside the PV ostia QMODE+ and QMODE may be used at the discretion of the Investigator.

### 8.2.3. Data Collection During Study Ablation Procedure

Procedural data collection will be done through generator files, CARTO® datafiles, procedural worksheets and subject medical files. Documentation of procedural data will be kept in the subject's CRF, back-up generator files and back-up CARTO® log files for study analysis.

At the completion of the study ablation procedure two back-up copies of the CARTO® 3 and generator log files will be made. One copy should be kept at the site within the investigator site or patient binders, and one fully anonymized copy will be sent to the sponsor, in a timely manner

The Carto and Generator data (electronic raw data) collected during the Study Ablation procedure will be anonymized (or de-identified) prior to its transfer to the Sponsor. Data will be verified during this lifecycle (Data Transfer) to ensure the records are complete and are traceable to subjects within each clinical site. Data will be archived per the applicable policies and procedures as it relates to Data Extract process, Record Retention etc., and will be the source for data analysis. During data transfer, redundant copies will be stored at each critical stage of the transfer to safeguard adequate control over business continuity or disaster recovery of records. A copy of the electronic raw data will also be stored at each clinical site until receipt and storage by the sponsor has been confirmed.

The information collected during the procedure will include, but will not be limited to, the list below.

- RF application-mode per lesion (QMODE+ /QMODE)
- Number of RF applications with QDOT MICRO™ catheter (total/QMODE+/QMODE)
- Duration of RF applications with QDOT MICRO™ catheter (total/QMODE+/QMODE)
- PVI ablation time (time between first RF application and last RF application on a PV before isolation confirmed and circumferential ablation achieved)
- Subject PVI ablation time (time between first RF application and last RF application before all PVI complete)
- Subject total ablation time (time between first RF application and last RF application in a subject)
- Ablation parameters per RF application from the generator files
- Touch-up applications
- Total procedure time (from first femoral puncture to last catheter removal)
- Mapping time
- Fluoroscopy time
- LA catheter dwell time (from ablation catheter LA insertion to ablation catheter removal from the LA)
- ECG data
- Total fluid delivered via ablation catheter and via intravenous line (if captured); fluid output and net fluid input (if captured)
- Strategy used to minimize risk of esophageal injury, if any
- Abnormal esophageal temperature rises (if captured)

### 8.2.4. Pre-Discharge Assessments

Prior to hospital discharge, the following assessments should be performed:

- **Cardiac medication and anticoagulation regimen** (only cardiac related AADs, anticoagulation regimen, etc.)
- **ECG** in case of standard of care
- **Adverse events**, if any

- **Occurrence of AF** or other arrhythmias, if any

## 8.3. Post-Ablation Follow-up Schedule and Final Study Visit

The subject will be required to complete follow up visit at 7 days (phone call or clinic visit) post procedure.

Discharged subjects will receive a telephone call or clinic visit at (7D, day -1 or +3) post ablation procedure to assess medication, AF occurrences and Adverse Events.

The subject will be required to complete follow up through 3 months post initial ablation procedure. The follow-up visit is 3 months ± 14 days (3M, day 76-104) post ablation procedure. Follow-up visit schedule should be based on the date of the index study ablation procedure and will not reset if subject undergoes a repeat AF ablation procedure.

- At the **3 months post ablation procedure visit** (in-clinic or telehealth visits) the following assessments should be performed:
    - **Cardiac medication and anticoagulation regimen** (only cardiac related AADs, anticoagulation regimen, etc.)
    - Medical / Hospitalization History
    - **ECG** at the discretion of the investigator
    - **Adverse events**, if any
    - **Assessment of AFL/AT/AF occurrence** and repeat ablation
    - **End of Study** Follow up

## 8.4. Early Termination Visit

Subjects may withdraw from the clinical investigation at any time. The decision for the subject to withdraw informed consent must be made independently of influence by the investigator or site personnel. The subject's decision will be documented in the source and eCRF. The investigator may also choose to withdraw a subject from the study if there are safety concerns. If a subject withdraws from the study, the date and reason for withdrawal will be recorded on the appropriate electronic case report form (eCRF).

All data will be collected (as available) until the subject is withdrawn. If the subject is withdrawn due to an adverse event (AE) or serious adverse event (SAE), the investigator should follow the subject until the AE/SAE has resolved or is considered stable. The local CHU will collect the resolution information of any reported SAEs.

## 8.5. Schedule of Events Table

This table displays the required schedule for subject treatments and evaluations. Subjects should undergo procedure within 60 days of signing informed consent.

**Table 4. Summary of Subject Assessments**

| **Assessments** | **Pre-ablation** | **Procedure** | **Pre-discharge** | **7D** (D6-10) | **M3** (D76-104) |
|---|---|---|---|---|---|
| Clinic visit | ● | ● | | | ● [1] |
| Phone Call | | | | ● [1] | |
| Patient Informed Consent[2] | ● | | | | |
| Demographics[2] | ● | | | | |
| Medical/AF history | ● | | | ● | ● |
| Cardiac and Anticoagulation Medications | ● | | ● | ● | ● |
| Ablation Assessment | | ● | | | |
| ECG | | | ● [5] | ● [1,5] | ● [1,5] |
| Pregnancy Test | ● [3] | | | | |
| LA thrombus detection | ● [2] | | | | |
| Adverse events/Device Deficiency[4] | ● | ● | ● | ● | ● |
| AF recurrences | | | ● | ● | ● |

1. May be conducted as a clinic visit (ECG performed if Clinic visit) or a telehealth visit.
2. To be completed within 48 hours prior to ablation procedure
3. In all women of childbearing age and potential. To be completed within one week prior to ablation procedure.
4. Device Deficiency to be collected at ablation and pre-discharge
5. If completed at the investigator's discretion.

# 9. Assessment of Safety

## 9.1. Specific Safety Parameters

### 9.1.1. Definition of Adverse Events (AE)

An AE is any untoward medical occurrence in a subject whether or not related to the medical device under study.

Specifically, an adverse event (AE) is **any** undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject during the course of the study, whether or not it is related to the device or procedure. Physical findings (including vital signs) observed at follow-up, or pre-existing physical findings that worsen compared to baseline, are considered adverse events.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. Such conditions should be added to background medical history, if not previously reported. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

AF recurrence by itself is considered a recurrence of disease (pre-existing condition), and, therefore, **does not meet the definition of an AE**. Recurrence of pre-existing AFL/ atrial tachycardia (AT) is also considered recurrence of disease and does not meet the definition of an AE.

The following clinical events **will not be considered an adverse event for this clinical study**:

- A trace / trivial pericardial effusion that is asymptomatic, requires no medical intervention, and does not extend hospitalization will not be considered an adverse event
- AF/AFL/AT recurrence requiring pharmacological or synchronized electrical cardioversion during the hospitalization for the index ablation procedure
- AF/AFL/AT recurrences throughout the duration of the study, as they will be reported as within the effectiveness analysis of early recurrences during the blanking period via arrhythmia monitoring data collection per consensus guidelines.
- However, the development of a new atrial arrhythmia deemed as not an effect of the ablation procedure (in example new onset of left atrial flutter occurring post-ablation) is an AE.
- Re-ablation for AF or preexisting AFL/AT itself is not an AE, however any procedural complication is considered an AE and shall be reported within the applicable timelines

### 9.1.2. Definition of Serious Adverse Event (SAE)

A serious adverse event (SAE) is **ANY** event that meets one or more of the following criteria:

- Leads to a death
- Leads to a serious deterioration in the health of a subject that resulted in:
  - A life-threatening illness or injury
  - An injury or permanent impairment of a body structure or a body function

- In-patient hospitalization or prolongation of an existing hospitalization*
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function

- Leads to fetal distress, fetal death or a congenital abnormality or birth defect.

*****Planned hospitalization for a condition present prior to the participant's enrollment in the study will not meet the definition of an SAE. An AE would meet the criterion of "hospitalization" if the event necessitated an admission to a health care facility (e.g., an overnight stay). Emergency room (ER) visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.

### 9.1.3. Adverse Device Effect (ADE) / Serious Adverse Device Effect (SADE)

An **Adverse Device Effect (ADE)** is an adverse event related to the use of the device under study.

NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device under study.
NOTE 2: This includes any event that is a result of a use error or intentional abnormal use of the investigational device under study.

A **Serious Adverse Device Effects (SADE)** is an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

### 9.1.4. Unanticipated (Serious) Adverse Device Effect (UADE/USADE)

An **unanticipated adverse device effect (UADE)** or **unanticipated serious adverse device effect (USADE)** is any serious adverse effect on health, safety, any life-threatening problem, or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the post market clinical follow up plan or risk analysis report, or any other unanticipated serious problem associated with a device that relates to rights, safety, or welfare of subjects.

Refer to Table 8 for a comprehensive list of foreseeable and anticipated adverse events.

### 9.1.5. Study Device Deficiency, Failure or Malfunction

A device has failed if it does not perform according to the IFU or fails to meet the expectations of the device and/or investigator (i.e., related to appearance of the device, performance, durability, safety, effectiveness, quality, reliability, labeling, etc.). If a device failure is detected or suspected, it should be documented on the appropriate eCRF and device failure and AE must be reported as soon as possible to the Sponsor per section 9.4.

## 9.2. Classification of an Adverse Event

### 9.2.1. Severity of Event

The intensity or severity of each AE must be assessed according to the following classifications:

**Table 5. Intensity or Severity Definitions**

| | |
|---|---|
| **Mild** | Awareness of signs, symptoms, or events that are otherwise easily tolerated that may result in minimal transient impairment of a body function or damage to a body structure, but do not require intervention other than monitoring. |
| **Moderate** | Any event that results in moderate transient impairment of a body function or damage to a body structure that causes interference with usual activities, or that warrants possible intervention, such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure. |
| **Severe** | Any event that is incapacitating (an inability to do usual activities) or is life-threatening and results in permanent impairment of a body function or damage to a body structure, or requires intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure. |

### 9.2.2. Relationship to Study Device

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

**Table 6. Adverse Event Causality Classifications**

| Caused By | Relationship | Definition of Relation |
|---|---|---|
| **Device** | **Causal** | The event is associated with the device under study beyond reasonable doubt |
| | **Probable** | The relationship with the use of the device under study seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained |
| | **Possibly** | The relationship with the use of the device under study is weak but cannot be ruled out completely |
| | **Unlikely** | The relationship with the use of the device under study seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained |
| | **Not Related** | Relationship to the device under study can be excluded |
| **Study Procedure** | **Causal** | The event is associated with the study procedure beyond reasonable doubt |
| | **Probable** | The relationship with the study procedure seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained |
| | **Possibly** | The relationship with the study procedure is weak but cannot be ruled out completely |
| | **Unlikely** | The relationship to the study procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained |
| | **Not Related** | Relationship to the procedure can be excluded |

### 9.2.3. Outcome

The outcome of each AE must be assessed according to the following classifications:

**Table 7. Adverse Event Outcome Classifications**

| Classification | | Definition |
|---|---|---|
| **Recovered** | **Resolved** | Subject fully recovered with no observable residual effects |
| | **Resolved with sequelae** | Subject recovered with observable residual effects |
| **Recovering** | **Resolving** | Adverse event has not resolved and additional change in condition is possible |
| **Not Recovered** | **Not Resolved** | Subject didn't recover from the AE and the observed AE effects are still present |
| **Fatal** | | Subject died as a result of the AE (whether or not the AE is related to the device or procedure) |

### 9.2.4. Anticipated Adverse Event

An anticipated Adverse Event is an effect which by nature, incidence, severity or outcome has been identified as a possible complication associated with the investigational medical device and/or intervention procedure.

Potential adverse events that are reasonably anticipated to occur during the cardiac electrophysiology procedure are listed in Table 8. These events should be reported via EDC as anticipated AEs.

**Table 8. Comprehensive List of Anticipated AEs**

| Anticipated Adverse Events | |
|---|---|
| Acute Respiratory Distress Syndrome (ARDS) | Air embolism |
| Allergic reaction | Allergic reaction to Anesthesia (e.g., hair loss) |
| Anaphylactic shock | Anemia |
| Anesthesia reaction | Apnea - sedation induced |
| Arrhythmia: bradycardia | Arrhythmia: pro-arrhythmias |
| Arrhythmia: tachycardia | Aspiration pneumonia |
| Asthmatic attack | Atelectasis |
| Atelectasis | Atrial fibrillation* |
| Atrio-Esophageal fistula | Atypical left atrial flutter |
| AV fistula | Bleeding complications |
| Bleeding requiring transfusion | Cardiac arrest |
| Cardiac perforation | Cardiac thrombo-embolism |
| Cerebro-vascular accident (CVA) / stroke | Chest pain/discomfort |
| Complete heart block, temporary or permanent | Conduction block: ongoing / resolved |

| | |
|---|---|
| Congestive Heart Failure | Coronary artery dissection |
| Coronary artery occlusion | Coronary artery spasm |
| Coronary artery Thrombosis | Damage to the vascular system |
| Death | Deep venous thrombosis |
| Diaphragmatic paralysis | Dislodgement of permanent pacing leads |
| Disseminated Intravascular Coagulation | Dyspnoea |
| Endocarditis | Epistaxis |
| Esophageal Injury | Exacerbation of pre-existing arrhythmia* |
| Expressive aphasia | Fainting |
| Fatigue | Gastric reflux |
| Gastrointestinal diverticulosis | Gastro-intestinal NOS |
| Heart Failure | Hematoma (local) /ecchymosis |
| Hemorrhage | Hemothorax |
| High / increased creatine phosphokinase (CPK) | Hypotension |
| Hypoxia | Increase in frequency or duration of episodes of typical atrial flutter |
| Increased phosphokinase level | Infection, localized |
| Infection, systemic | Injury to skin, muscle, connective tissue due to body position, electrical cardioversion, etc. |
| Laceration | Leakage of air or blood into the lungs or other organs due to perforation |
| Liver toxicity | Mobile strands in Inferior Vena Cava |
| Myocardial Infarction | Nausea |
| Neurological disorders (headache) | Neurological disorders (poor coordination) |
| Neurological disorders (tremor) | Obstruction to the vascular system |
| Palpitations | Perforation to the vascular system |
| Pericardial effusion without tamponade | Pericardial effusion resulting in tamponade |
| Peripheral embolus | Pericarditis |
| Peripheral thromboembolism | Peripheral nerve injury |
| Phrenic nerve damage | Phlebitis |
| Pneumothorax | Pleural effusion |
| Pulmonary edema | Pseudoaneurysm |
| Pulmonary hypertension | Pulmonary embolism |
| Pulmonary vein dissection | Pulmonary toxicity, like acute pulmonary syndrome |
| Pulmonary vein thrombus | Pulmonary vein Stenosis |
| Renal failure | Pump failure |
| Respiratory failure | Respiratory depression |
| Rhabdomyolysis, including produced by body position or propofol | Retroperitoneal hematoma |
| Seizure | Sedation induced $CO_2$ retention with lethargy and cholecystitis |
| Skin burns (due to cardioversion, tape, etc) | Sepsis |

| | |
|---|---|
| Skin injury / muscle or connective tissue injury due to body position, electrical cardioversion | Skin discoloration |
| Tamponade | Skin rash |
| Thrombocytopenia | Temperature elevation |
| Thrombosis | Thromboembolism |
| Transient extremity numbness | Thyroid disorders |
| Unintended complete or incomplete AV, Sinus node, or other heart block or damage | Transient ischemic attack (TIA) |
| Urinary tract injury or infection related to the urinary catheter | Urinary retention |
| Vasovagal reactions | Valvular damage/insufficiency |
| Volume overload | Vision change |
| X-ray radiation injury of skin, muscle and/or organ | Worsening obstructive, restrictive, or other form of pulmonary disease |

*Atrial Fibrillation and exacerbation of an existing arrhythmia are anticipated adverse events. However, they will not be captured as such under this protocol, as they are considered recurrence of disease.

## 9.3. Time Period and Frequency for Event Assessment and Follow-up

The investigator, or designated individual, will record all reportable events with start dates occurring any time after informed consent is obtained. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit.

All AE/SAEs need to be followed until the event is resolved (with or without sequelae). The medical monitor or designee of this clinical investigation will decide if more follow up information is needed in case the event is not resolved at study completion. All required treatments and outcomes of the (S)AE must be recorded in the eCRF. Additional documentation may be requested by the Sponsor or designee, including but not limited to, a written subject narrative detailing the clinical course of the AE/incident, a copy of any correspondence with the local REB, hospital records, death certificate and autopsy report if available. The local CHU will collect the resolution information of any reported SAEs.

## 9.4. Reporting Procedures

### 9.4.1. Adverse Event Documentation and Reporting Requirements

Subjects should be encouraged to report AEs spontaneously or in response to general, non-directed questioning (e.g. “How was your health been since last visit?”). Anytime during the study, the subject may volunteer information that resembles an AE.

Each AE must be reported to the sponsor regardless of classification, seriousness, intensity, outcome or causality. The investigator is responsible for ensuring that all AEs observed by the investigator, or reported by the subject, that occur from the time that the subject has signed the informed consent through the end of the study are properly assessed, recorded, and reported as defined and described in the AEs, Adverse Device Effects and Device Deficiencies section of this protocol. All adverse events must be documented by completing subject’s medical records (source documents) and appropriate eCRF by the investigator or study coordinator throughout

the study and provided to the Sponsor. All AEs will be monitored until they are adequately resolved or explained.

Anonymized documentation pertaining to the AE (e.g. laboratory tests, consultation reports, post-mortem reports, new information relating to a previously reported AE, correspondence with the local EC, etc.) will be provided by the investigator to the sponsor or designee in a timely manner, when requested. Follow-up reports relative to the subject's subsequent course must be submitted to the sponsor or designee until the event has resolved or, in case of permanent impairment, until the condition stabilizes. If the subject is withdrawn from the study because of the AE, the information must be included on the appropriate eCRFs.

The sponsor is responsible for the classification of AEs and ongoing safety evaluation of the study and shall review the investigator's assessment of all AEs. The sponsor will determine and document in writing their seriousness and relationship to the investigational device. In case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to the concerned parties.

Biosense Webster will ensure that investigators are instructed to return devices suspected of causing an AE or SAE (i.e., definitely device-related or possibly device-related) in accordance with relevant regulations and current company procedures.

In the case of serious device effects and device deficiencies that could have led to serious adverse device effects, the Sponsor will determine whether the risk analysis needs to be updated and whether corrective or preventative action is required.

Timing for reporting the different types of AEs is described in Table 9.

**Table 9. AE Reporting Requirements**

| Type of Adverse Event | Reporting Requirements |
|---|---|
| Serious Adverse Events | Report to Sponsor immediately upon awareness of event but no later than 72 hours |
| USADE & SADE | Report to Sponsor immediately upon awareness of event but no later than 72 hours |
| Primary AEs | Report to Sponsor immediately upon awareness of event but no later than 72 hours |
| Study device failure/malfunction associated with an AE | Report both study device failure and AE to Sponsor immediately upon awareness of event but no later than 72 hours |
| All other Adverse Events | Report to Sponsor within 2 weeks upon awareness of the event |

### 9.4.2. Incident Reporting

All Adverse Event will be reviewed by the Complaint Handling Unit (CHU) of the Sponsor, where the assessment will be made if the respective event is reportable as required by Health Canada.

The sponsor will submit as per site specific requirements in a timely manner to all participating clinical investigators, a safety overview. Pursuant to EN ISO 14155AEs will be fully

recorded and reported by the sponsor to Health Canada as well as the REB according to the requirements and deadlines in force.

### 9.4.3. Events of Special Interest

Event reporting to Health Canada in accordance with the jurisdictional regulations will occur by the sponsor and/or by the investigator, depending upon the local requirements.

A device deficiency related to a medical device not manufactured by Biosense Webster should be reported by the investigator to their respective manufacturer as per relevant regulation. Complaints related to non-Biosense Webster, Inc. products must be handled according to institutional policies, HC policies, and local regulations.

## 9.5. Safety Oversight

Safety oversight will be conducted by the Medical Safety group. Aggregate safety data will be reviewed during enrollment by the study safety lead in order to promptly identify new issues or trends which may have an impact on the conduct of the study and/or subject safety. As deemed applicable, under the rules of an approved study-specific charter, safety events might be reviewed by an established committee which may recommend appropriate action(s) to ensure subject safety.

# 10. Administrative Responsibilities

## 10.1. Ethics Committee and Competent Authority Application

The study protocol (or amendment[s]), ICF, and other applicable study related documents must be approved by HC before enrollment of subjects. Any additional requirement imposed by the EC or regulatory authority shall be discussed, agreed upon, and followed. A signed copy of the EC and CA (if applicable) approval letters addressed to the investigator must be submitted to Biosense Webster certifying study approval prior to subject enrollment. Biosense Webster and the EC must approve, in writing, any changes to the protocol that affect the rights safety and/or welfare of the subjects, or may adversely affect the validity of the study.

## 10.2. Audits and Inspections

The sponsor and/or designee and/or Regulatory Authorities may contact the participating institution to inform the investigator of an upcoming audit/inspection. The investigator should immediately notify the sponsor of any Regulatory Authority audits/inspection at the study site. The audit/inspection can include the review of documents, facilities, records and any other resources deemed by the authorities to be related to study.

# 11. Deviations from the Clinical Study Plan

The investigator is responsible for ensuring that the clinical investigation is conducted in accordance with the procedures and evaluations described in this protocol. The study monitors shall verify that the conduct of the study is in compliance with the currently approved protocol and applicable regulations, and shall identify any issues of non-compliance with regulations or guidelines.

Issues of non-compliance include but are not limited to repeated protocol deviations; failure to obtain proper informed consent; non-conformance to EC requirements; failure to report Adverse Events, product malfunctions and other product issues; and other non-conformance to GCPs.

A protocol deviation is defined as an instance of failure to follow, intentionally or unintentionally, the requirements of the protocol (e.g. missed test or procedure, visit out of window, non-adherence to inclusion/exclusion criteria). Investigators are not allowed to deviate from the protocol. Protocol deviations will be monitored closely and will be reported per EC/CA requirement.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of a subject may proceed without prior approval of the sponsor and EC. Such deviations shall be documented and reported to the sponsor and the EC as required.

All instructions described in this study protocol are to be followed. If an amendment is required, it must be made in written form and receive approval from all persons and authorities who approved the original protocol. Administrative changes (do not affect subject's benefits/risks ratio) may be inserted with abbreviated approval. All amendments will be distributed to all original protocol recipients.

# 12. Investigational Product Accountability

# 13. Clinical Monitoring

Clinical site/remote (targeted) monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). Each site might undergo periodic monitoring of the study, which might involve a visit from a Sponsor representative, qualified to perform such visit.

Monitoring contacts (visits or remote) may include, but are not limited to, the following:

- Protocol adherence
- Source documentation verification and accuracy of the eCRFs
- Verification that informed consent is being obtained for all subjects participating in the study in accordance with requirements described in the study protocol
- Verification of completeness of the Site File
- Verification of accuracy of all study logs such as the Delegation of Responsibility Log, etc.
- Compliance with applicable regulations
- Identification and action to resolve any issues or problems with the study.

Data are to be submitted promptly via e-CRF after collection. Missing or unclear data will be corrected as necessary throughout the trial. Biosense Webster will request further documentation such as physician and/or cardiac EP lab procedure notes when complications or malfunctions are observed and reported.

Further details on clinical monitoring are provided in the study specific monitoring plan.

# 14. Statistical Methodology

The Sponsor will be responsible for the overall analysis of data from this protocol. This section represents the Statistical Analysis Plan for this protocol. All analyses and subsequent detail are described below.

## 14.1. Levels of Significance

All data will be summarized by descriptive analyses. No formal statistical inference will be made.

## 14.2. Analysis Sets

The following analysis populations will be used to complete the analyses of data:

- **Safety Analysis Set**: The Safety Analysis Set will include all enrolled subjects who have the investigational device inserted, regardless if RF energy is delivered.

- **Effectiveness Analysis Set** : The effectiveness analysis set will include all enrolled subjects who meet the study eligibility criteria, have the investigational device inserted and undergo an ablation procedure with the study catheter used in conjunction with QMODE+ and /or QMODE for PVI (RF energy is delivered). The subjects without any QMODE+ applications for PVI will be considered a failure.

## 14.3. Sample Size Justification

Since this study is a workflow study with no primary hypotheses to be tested, there are no statistical power calculations. Evidence from between 30 to 50 prospectively enrolled subjects are deemed sufficient to characterize safety and performance of the Qdot-nGen ablation system.

## 14.4. Analyses to be conducted

### 14.4.1. General Conventions

Standard descriptive summaries for continuous data include the number of observations with data, mean, standard deviation (SD), median, minimum, and maximum values. The mean and median will be rounded to one decimal place greater than in the raw data where applicable; the standard deviation will be rounded to two decimal places greater than in the raw data where applicable. In cases where this is not applicable (e.g., average time spent), the mean will be rounded to one decimal place; the standard deviation to two decimal places; the minimum and maximum to the nearest whole number. These will be referred to as “continuous summaries” in this document.

For categorical data, the count and percent will be provided. Percentages will be based on the number of subjects without missing data. For adverse event and device effects data, percentages will be based on the number of subjects in the analysis population being used in the analysis. When count data are presented, the percentage for zero counts will be suppressed in order to draw attention to the non-zero counts. Frequency counts will be presented as whole numbers and

percentages will be rounded to one decimal place. This will be referred to as "categorical summaries" in this document.

Adverse events (AE) tables will be sorted by decreasing frequency of events, unless otherwise specified.

### 14.4.2. Disposition of Study Subjects

Subject disposition of will be summarized using categorical summaries. The number and percent of patients who were enrolled in the study, excluded from the study, included in the safety, and effectiveness analysis set, completed the study, and prematurely discontinued from the study will be presented. Patients who prematurely discontinued will be summarized by number and percentage by primary reason for discontinuation.

A listing of subject disposition will be generated as well as flow diagrams.

### 14.4.3. Demographic and Baseline Characteristics

All demographic and baseline characteristics will be summarized using categorical and continuous summaries, as appropriate, for all the safety analysis set.

A listing of subject demographic and baseline characteristics will be generated.

### 14.4.4. Analysis for Primary Endpoint

Acute procedural success will be summarized using categorical summaries for the effectiveness analysis set.

A listing of the primary endpoint will be provided.

### 14.4.5. Analyses of Additional Endpoints

All analyses of additional endpoints will use the effectiveness analysis set.

Procedural parameters (Total procedure time, Mapping time, PV ablation time, Total ablation time, RF application time, and Total Fluoroscopy time) will be analyzed using the safety analysis set using continuous summaries.

Procedural data measures (Catheter ablations outside the PV area, PVI achieved with QMODE+ only among all targeted veins and by subject, PVI achieved with combined use of QMODE+ and QMODE among all targeted veins and by subject, Need for ablation of acute PV reconnection (touch-up) among all targeted veins and by subject, Total number of RF applications, % QMODE+ applications and % QMODE applications, Anatomical location of touch-up applications using the QDOT catheter, and Confirmation of RF energy delivery from nGEN log files) will be summarized using categorical summaries.

Procedural details will be summarized as follows. Temperature, power, contact force, and impedance during RF application will be summarized using continuous summaries. Anatomical segment location per RF application will be summarized using categorical summaries.

Listings of additional endpoints will be generated.

### 14.4.6. Analyses of Secondary Safety Endpoints

Secondary safety endpoints will be analyzed using the safety analysis population.

An adverse event (AE) is an event recorded on the Adverse Event CRF page with an onset on or after the study ablation procedure. AEs with onset prior to this date that worsen in severity (i.e., increases in severity) after a subject has signed informed consent OR have a missing onset date are also considered an AE. AEs will be summarized both by subject and event. If a subject has multiple occurrences of an AE, for the by-subject summary only a single occurrence will be counted and for the by-event summary each event will be counted.

The overall incidence of AEs will be summarized by:

- Any adverse event;
- Serious adverse event;
- Non-serious adverse event;
- Device-related adverse event (defined as unlikely, possible, probable or having a causal relationship with the device);
- Serious device-related adverse event;
- Unanticipated device-related adverse event;
- Serious unanticipated device-related adverse event;
- Procedure-related adverse event (defined as unlikely, possible, probable or having a causal relationship with the procedure);
- Adverse events leading to discontinuation.

Serious AEs (SAE) and Non-Serious AEs (NSAE) will be summarized separately by overall incidence and adverse event term using categorical summaries.

An adverse device effect (ADE) is any event recorded to have led to an AE on the Investigational device deficiency CRF.

ADEs will be summarized by overall incidence, ADEs leading to an AE, ADEs leading to an SADE and unanticipated SADE (USADE), device, and time point during the procedure using categorical summaries.

Serious Adverse ADEs (SADE) will be summarized by overall incidence, SADEs leading to an AE, SADEs leading to a USADE, device, and time point during the procedure using categorical summaries.

ADEs, SADEs, and USADEs will be summarized by overall incidence and by adverse event term using categorical summaries in separate tables.

Listings of adverse events and device effects will be generated as well as device deficiencies.

### 14.4.7. Handling of Missing Data

Missing data will not be imputed. All analyses will be performed using observed data.

# 15. Ethics and Protection of Human Subjects

## 15.1. Ethical Standard

As the Sponsor of this study, Biosense Webster has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration and the local government (Health Canada). The Sponsor will also maintain compliance with Good Clinical Practice (ICH version 4 du 1 May 1996), the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, Tokyo 2004), Sponsor general duties (21 CFR 812.40), selection of investigators (21 CFR 812.43), monitoring (21 CFR 812.46), supplemental applications (21 CFR 812.35 [a] and [b]), maintaining records (21 CFR 812.140 [b]), and submitting reports (21 CFR 812.150 [b)]), and to local regulations where required.

- **General Duties**
  Biosense Webster's general duties consist of submitting the clinical investigation application to appropriate regulatory agencies, assuring that sites have received EC approvals prior to shipping the devices, selecting investigators, ensuring proper clinical site monitoring and ensuring subject informed consent is obtained.

- **Data Quality and Reporting**
  Biosense Webster is responsible for providing quality data that satisfy federal regulations and informing proper authorities of serious unanticipated adverse events (SADE's)and deviations from the protocol.

- **Selection of Investigators**
  All potential investigational sites will undergo an evaluation to ensure that the site has the appropriate facilities and personnel to conduct the study in compliance with the clinical post market clinical follow up plan. Based on outcome of evaluation process, Biosense Webster will select qualified investigators, ship devices only to participating investigators, obtain a signed Investigator's Agreement and provide the investigators with the information necessary to conduct the study.

- **Supplemental Applications**
  As appropriate, Biosense Webster will submit changes in the clinical post market clinical follow up plan to the investigators to obtain all applicable re-approvals.

- **Maintaining Records**
  Biosense Webster will maintain copies of correspondence, data, adverse device effects and other records related to the study. Biosense Webster will maintain records related to the signed Investigator Agreements.

- **Submitting Reports**
  Biosense Webster will submit any required regulatory reports identified in this section of the regulation. This may include unanticipated adverse device effects, withdrawal of EC approval, current investigators list, annual progress reports, recall information, final reports and protocol deviations.

## 15.2. Informed Consent Process

Subjects informed consent must be obtained and documented according to the principles of informed consent in the latest version of the Declaration of Helsinki (Brazil, 2013), ISO 14155:2011, and approved by the reviewing Regulatory Authority and EC.

Informed consent is mandatory and must be obtained from all subjects prior to their participation in the study.

Prior to screening or performing any study related procedures that are solely for the purpose of determining eligibility for this study, any potential benefits and risks of the study must be explained to the subject. Subjects will be informed about aspects of the study that are relevant to the subject's decision to participate. Subjects should be made aware that by signing the Informed Consent Form (ICF), they are granting approval for study personnel to review their medical records and to collect/analyze personal medical information. Subjects should also be informed that study personnel will always maintain confidentiality of the medical records.

The ICF will be written in a native, non-technical, language that is understandable to the subject and is to be approved by the applicable EC prior to enrolling subjects. The subject or designee will be provided with ample time to read and understand the ICF and to consider participation in the study. Informed consent will be requested prior to enrollment and must be personally signed and dated by the subject, or subject's legal representative, prior to performance of any study related activity or procedure. If a subject is unable to read or write, informed consent shall be obtained through the aid of an independent witness who will be present throughout the process. The written ICF and any other information shall be read aloud and explained to the prospective subject and, whenever possible, subject shall sign and date the ICF. The witness must also sign and date the ICF attesting that the information was accurately explained, and that informed consent was freely given. The point of enrollment corresponds with the time that subjects signs the informed consent.

The investigator and/or designee must also clearly document the process of obtaining informed consent in the subject's source documents. The voluntary process of obtaining informed consent confirms the subject's willingness to participate in the study. It's the investigator's responsibility to ensure that the informed consent process is performed in accordance with ICH-GCP and, where applicable, local and federal regulations. Subjects should not be coerced, persuaded, or unduly influenced to participate or continue to participate in the trial. Subjects or his/her legal representative must be given ample time and opportunity to inquire about details of the trial and all questions about the trial should be answered to the satisfaction of the patient or the representative. Failure to provide written informed consent renders the subject ineligible for the study. If new information becomes available that can significantly affect a subject's future health and/or medical care, this information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing by dating and signing the amended ICF.

## 15.3. Participant and Data Confidentiality

During this clinical investigation, all representatives of the Sponsor will comply with all in-country privacy laws and regulations regarding contact with subjects, their medical record information, copying of information, and protection of the subject identities.

All information and data sent to Biosense Webster concerning subjects or their participation in this clinical investigation will be considered confidential. Only authorized Biosense Webster personnel or representatives (including contracted service providers, i.e. Core Lab, Clinical Research Associate, CRO, etc.), representatives of the FDA or Competent Authorities acting in their official capacities will have access to these confidential files upon request (including, but not limited to, laboratory test result reports, ECG reports, admissions/discharge summaries for hospital admission occurring during a patient's study participation and autopsy reports for deaths occurring during the clinical investigation). Some of the countries to which the study subjects and investigators personal data may be transferred may not offer as comprehensive a level of protection of personal data as within the Canada but Sponsor will take all reasonable steps to ensure a sufficient level of data protection. All data used in the analysis and reporting of this evaluation will exclude identifiable reference to the subject.

### 15.3.1. Research use of Stored Data

- Intended Use: Data collected under this protocol may be used to study Atrial Fibrillation.

- Storage: Access to stored data will be limited. Data will be stored using codes assigned by the sponsor. Data will be kept in password-protected computers. Only investigators and the sponsor will have access to the data.

## 16. Source Documents and Access to Source Data/Documents

Data entered on to the eCRFs will be taken from source documentation, such as hospital procedure reports, admission and discharge summaries, other hospital or investigator office/clinic documents, and system data (CARTO® 3, generator). If unique study parameters are not documented on standard hospital or office reports, a worksheet may be developed to record this information. The worksheet shall be signed by the PI or authorized designee and will serve as source document and as basis for monitoring the eCRFs. Electronic subject records will be considered as source documents on the condition that the hospital's database is a validated system. If this is not the case, electronic records should be printed and added to the subject's paper file. A print-out of a completed eCRF cannot be used as source documentation.

Investigators should maintain information in the subject's medical records, which corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained.

- Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol selection criteria (if not already present).
- Dated and signed notes from the day of entry into the study including the study Sponsor (Biosense Webster), protocol number, clinical site, subject number assigned and a statement that consent to participate in the study was obtained.
- Dated and signed notes from each study visit with reference to the eCRFs for further information, if appropriate (for specific results of procedures and exams).
- Reports on AEs and their resolution, including supporting documents such as discharge summaries, EP lab reports, ECGs, lab results.
- Notes regarding protocol-required medication and prescription medications taken during the study (including start and stop dates).
- Notes on subject's condition upon completion of or withdrawal from the study.

Only authorized Biosense Webster personnel or representatives, authorized site personnel, local government authorities, or the FDA, acting in their official capacities, will have access to these confidential files.

# 17. Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and ongoing QC checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, monitors will verify that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. If noncompliance is identified, Sponsor is required by regulation to implement measures to secure compliance.

The participating site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

# 18. Data Handling and Record Keeping

## 18.1. Data Collection and Management Responsibility

The Sponsor will be responsible for all data management activities. These activities include development of an electronic data collection (EDC) system and utilizing a validated EDC system into which all study data will be entered. The Sponsor will be responsible for reviewing all data to ensure the overall integrity of the database.

### 18.1.1. Data Collection

Electronic Case Report Forms (eCRFs) will be used to collect all subject data during this clinical investigation. eCRFs have been developed to capture the information outlined in this clinical investigation plan. Modification to the eCRF will only be made if deemed necessary by the sponsor. Data on these eCRFs will be monitored (source verified) and the monitor will ask the site representative to correct, if necessary, to match the source documents. All changes made to the data will be tracked in the electronic audit trail. The investigator will be required to sign designated eCRFs as verification that they have been reviewed and the data entered are correct. Data from these eCRFs will be used to provide analysis of this clinical investigation.

All CARTO® 3 (Version 6.0 or above) and nGEN Generator log files created during the procedure will be downloaded/ extracted and an anonymized copy provided to the sponsor for further evaluation.

### 18.1.2. Data Reporting

The investigator, or a designated individual, is responsible for ensuring that clinical investigation data are timely and properly recorded on each subject's eCRF and related documents. The investigator, or a designated individual, is required to electronically sign the eCRF on the appropriate pages to verify that he/she has reviewed and attests to the correctness of the recorded data. Completed eCRF will be reviewed and monitored by the sponsor personnel, or an

appropriately qualified and trained designee, throughout the clinical investigation. To this end, the Investigator and institution must permit inspection of the trial files and subject eCRFs by such representatives and/or responsible government agencies.

Investigators are required to prepare and submit accurate and timely reports on this study to the governing HC and Biosense Webster.

**Table 10. Responsibilities for Preparing and Submitting Reports**

| Type of Report | Prepared by Investigator For | Time of Notification |
|---|---|---|
| Subject withdrawal | Biosense Webster | Should report within 5 working days |
| Withdrawal of EC approval | Biosense Webster | Should report within 5 working days |
| Final report | Biosense Webster, EC | Will prepare a final report for the clinical investigation as required per national regulations. |
| Informed consent not obtained from subject | Biosense Webster, EC | Should report within 5 working days |

It is recommended that all eCRF data be entered by the designated site personnel as soon as possible. For AE reporting, refer to the Adverse Event Reporting Requirements and timelines noted within this clinical investigation protocol.

### 18.1.3. Data Verification and Review

Biosense Webster will track the amount of missing data and contact sites as appropriate to instruct them on steps to minimize missing data and remain compliant with protocol required assessments Missing or unclear data will be queried as necessary throughout the trial. Biosense Webster will request further documentation such as physician and/or cardiac EP lab procedure notes when complications or device malfunctions/complaints are observed and reported. Biosense Webster will be responsible for auditing the database and confirming the overall integrity of the data.

### 18.1.4. Final Data Analysis

All exported datasets for analyses will undergo a final data review before final database lock. Once all critical data are monitored and locked, the final analyses of clinical investigation data will be performed.

## 18.2. Study Record Retention and Archiving

Records and reports for the study will remain on file at the site for a minimum of five (5) years or per local and country specific record retention requirements following notification by the sponsor that all investigations have been terminated or completed. The sponsor must approve archiving, transfer, and destruction of the documentation, in writing, prior to the actual archiving, transfer, and destruction. The investigator must notify the sponsor, in writing, of transfer location, duration, and the procedure for accessing the study documentation.

If the investigator retires, relocates, or withdraws from assuming primary responsibility for keeping the study records, custody transfer per written notice must be submitted to the sponsor indicating the name and address of the person accepting primary responsibility. The EC must be notified in

writing of the name and address of the new custodian. Record retention dates must be provided to all parties by the sponsor's corporation.

# 19. Study Suspension or Termination

This study may be temporarily suspended or prematurely terminated at the discretion of the Sponsor. The Sponsor may also terminate a site prior to study completion if the Sponsor believes the site is no longer capable of participating (e.g., cannot fulfill subject enrollment or protocol compliance goals, site suspension by HC). If the study is prematurely terminated or suspended, the PI will promptly inform the EC and will provide the reason(s) for the termination or suspension.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The principal investigator and sponsor shall keep each other informed of any communication received from either the EC or the regulatory authority.

If early termination of the study is required due to safety concerns or the occurrence of unanticipated adverse or device events, each site will undergo a monitoring visit or call to conclude any outstanding issues, collect all outstanding CRF information, verify device accountability, and discuss any other items relevant to the conclusion of the study. Any enrolled subjects will continue to be followed per the study protocol requirements.

If, for any reason, the sponsor suspends or prematurely terminates the study at an individual study site, the sponsor shall inform the responsible regulatory authority as appropriate and ensure that the EC is notified, either by the principal investigator or by the sponsor. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other principal investigators.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, EC and/or regulatory agency.

# 20. Data and Publication Policy

Publications and/or presentation of clinical investigation results will be coordinated between Biosense Webster, Inc. and the clinical investigation author(s). Authorship will be determined prior to development of any manuscript.

All information concerning the study, device under study, sponsor operations, patent application, manufacturing processes, and basic scientific data supplied by the sponsor to the investigator and not previously published, are considered confidential and remain the sole property of the sponsor.

# 21. Document Filing

A copy of all approved versions of the Investigation Protocol will be kept, by the site, in the Investigator Site File and in the Sponsor Trial Master File.

# 22. Scientific References

1. Cain, M.E., *Atrial fibrillation--rhythm or rate control.* N Engl J Med, 2002. **347**(23): p. 1822-3.
2. Calkins, H., et al., *2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary.* J Arrhythm, 2017. **33**(5): p. 369-409.
3. Fuster, V., et al., *ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society.* Europace, 2006. **8**(9): p. 651-745.
4. January, C.T., et al., *2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society.* J Am Coll Cardiol, 2014. **64**(21): p. e1-76.
5. Jazayeri, M.R., et al., *Selective transcatheter ablation of the fast and slow pathways using radiofrequency energy in patients with atrioventricular nodal reentrant tachycardia.* Circulation, 1992. **85**(4): p. 1318-28.
6. Pappone, C., et al., *A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study.* J Am Coll Cardiol, 2006. **48**(11): p. 2340-7.
7. Wilber, D.J., et al., *Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial.* JAMA, 2010. **303**(4): p. 333-40.
8. Ullah, W., et al., *Randomized trial comparing pulmonary vein isolation using the SmartTouch catheter with or without real-time contact force data.* Heart Rhythm, 2016. **13**(9): p. 1761-7.
9. Kautzner, J., et al., *EFFICAS II: optimization of catheter contact force improves outcome of pulmonary vein isolation for paroxysmal atrial fibrillation.* Europace, 2015. **17**(8): p. 1229-35.
10. Andrade, J.G., et al., *Pulmonary vein isolation using "contact force" ablation: the effect on dormant conduction and long-term freedom from recurrent atrial fibrillation--a prospective study.* Heart Rhythm, 2014. **11**(11): p. 1919-24.
11. Anter, E., et al., *Acute pulmonary vein reconnection is a predictor of atrial fibrillation recurrence following pulmonary vein isolation.* J Interv Card Electrophysiol, 2014. **39**(3): p. 225-32.
12. Haines, D.E., *The biophysics of radiofrequency catheter ablation in the heart: the importance of temperature monitoring.* Pacing Clin Electrophysiol, 1993. **16**(3 Pt 2): p. 586-91.
13. Bhaskaran, A., et al., *Five seconds of 50-60 W radio frequency atrial ablations were transmural and safe: an in vitro mechanistic assessment and force-controlled in vivo validation.* Europace, 2017. **19**(5): p. 874-880.
14. Kuck, K.H., et al., *A novel radiofrequency ablation catheter using contact force sensing: Toccata study.* Heart Rhythm, 2012. **9**(1): p. 18-23.
15. Ikeda, A.N., H; Sharma, T; Govari, A; Datta, K; Joshi, H; Lifshitz, A; Wittkampf, F and Jackman, W, *High Power - Short Radiofrequency Applications Rapidly Produce Shallow Lesions Of Equal Diameter Without Increasing Risk Of Thrombus Or Steam Pop*, in *Heart Rhythm Society*. 2018: Boston, MA.
16. leshem, E., Zilberman I, Tschabrunn C, et al, *High-Power and Short-Duration Ablation for Pulmonary Vein Isolation Biophysical Characterization.* JACC: Clinical Electrophysiology, 2018. **In Press**.
17. Sandhu, R.K., et al., *The epidemiology of atrial fibrillation in adults depends on locale of diagnosis.* Am Heart J, 2011. **161**(5): p. 986-992 e1.
18. Lee, G., et al., *Low risk of major complications associated with pulmonary vein antral isolation for atrial fibrillation: results of 500 consecutive ablation procedures in patients with low prevalence of structural heart disease from a single center.* J Cardiovasc Electrophysiol, 2011. **22**(2): p. 163-8.

19. Voskoboinik, A., et al., *Low Rates of Major Complications for Radiofrequency Ablation of Atrial Fibrillation Maintained Over 14 Years: A Single Centre Experience of 2750 Consecutive Cases.* Heart Lung Circ, 2018.
20. Bohnen, M., et al., *Incidence and predictors of major complications from contemporary catheter ablation to treat cardiac arrhythmias.* Heart Rhythm, 2011. **8**(11): p. 1661-6.
21. Cappato, R., et al., *Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation.* Circ Arrhythm Electrophysiol, 2010. **3**(1): p. 32-8.
22. Michowitz, Y., et al., *Effects of sex on the incidence of cardiac tamponade after catheter ablation of atrial fibrillation: results from a worldwide survey in 34 943 atrial fibrillation ablation procedures.* Circ Arrhythm Electrophysiol, 2014. **7**(2): p. 274-80.
23. Muthalaly, R.G., et al., *Temporal trends in safety and complication rates of catheter ablation for atrial fibrillation.* J Cardiovasc Electrophysiol, 2018.
24. Teunissen C, V.B., Hassink, R, et.al, *Incidence of Pulmonary Vein Stenosis After Radiofrequency Catheter Ablation of Atrial Fibrillation.* JACC: Clinical Electrophysiology, 2017. **3**(6): p. 589-598.
25. Ha, F.J., et al., *Prevalence and prevention of oesophageal injury during atrial fibrillation ablation: a systematic review and meta-analysis.* Europace, 2018.
26. Knopp, H., et al., *Incidental and ablation-induced findings during upper gastrointestinal endoscopy in patients after ablation of atrial fibrillation: a retrospective study of 425 patients.* Heart Rhythm, 2014. **11**(4): p. 574-8.
27. Kapur, S., et al., *Esophageal Injury and Atrioesophageal Fistula Caused by Ablation for Atrial Fibrillation.* Circulation, 2017. **136**(13): p. 1247-1255.
28. Nair, K.K., et al., *Atrioesophageal Fistula: A Review.* J Atr Fibrillation, 2015. **8**(3): p. 1331.
29. Scanavacca, M.I., *How to prevent, recognize and manage complications of AF ablation?* Rev Port Cardiol, 2017. **36 Suppl 1**: p. 43-49.
30. Yong Ji, S., et al., *Phrenic nerve injury: An underrecognized and potentially preventable complication of pulmonary vein isolation using a wide-area circumferential ablation approach.* J Cardiovasc Electrophysiol, 2013. **24**(10): p. 1086-91.
31. Cappato, R., et al., *Prevalence and causes of fatal outcome in catheter ablation of atrial fibrillation.* J Am Coll Cardiol, 2009. **53**(19): p. 1798-803.
32. Haegeli, L.M. and H. Calkins, *Catheter ablation of atrial fibrillation: an update.* Eur Heart J, 2014. **35**(36): p. 2454-9.
33. Funayama, N., et al., *Acute right coronary artery occlusion after radiofrequency catheter ablation of cavotricuspid isthmus: Vascular response assessed by optical frequency domain imaging.* HeartRhythm Case Rep, 2017. **3**(10): p. 496-498.
34. Rillig, A., et al., *Catheter ablation within the sinus of Valsalva--a safe and effective approach for treatment of atrial and ventricular tachycardias.* Heart Rhythm, 2008. **5**(9): p. 1265-72.
35. Fujii, S., J.R. Zhou, and A. Dhir, *Anesthesia for Cardiac Ablation.* J Cardiothorac Vasc Anesth, 2017.
36. Liu, Y., et al., *Incidence and outcomes of cerebrovascular events complicating catheter ablation for atrial fibrillation.* Europace, 2016. **18**(9): p. 1357-65.
37. Bessiere, F. and P. Chevalier, *Pulmonary vein hematoma after atrial fibrillation cryoablation: a new complication.* Heart Rhythm, 2013. **10**(9): p. 1359.
38. De, S.C., et al., *Direct Pulmonary Vein Ablation With Stenosis Prevention Therapy.* J Cardiovasc Electrophysiol, 2015. **26**(9): p. 1000-1006.
39. Lin, A.C. and D. Wilber, *Complications associated with radiofrequency catheter ablation*, in *Radiofrequency Catheter Ablation of Cardiac Arrhythmias: Basic Concepts and Clinical Applications*, S.K.S. Huang and D.J. Wilber, Editors. 2000, Futura Publishing Company, Inc.: Grouponk, NY. p. 737-746.
40. Scheinman, M.M. and S. Huang, *The 1998 NASPE prospective catheter ablation registry.* Pacing Clin Electrophysiol, 2000. **23**(6): p. 1020-8.
41. Calkins, H., et al., *Radiation exposure during radiofrequency catheter ablation of accessory atrioventricular connections.* Circulation, 1991. **84**(6): p. 2376-82.

42. Kovoor, P., et al., *Risk to patients from radiation associated with radiofrequency ablation for supraventricular tachycardia.* Circulation, 1998. **98**(15): p. 1534-40.
43. Nahass, G.T., *Fluoroscopy and the skin: implications for radiofrequency catheter ablation.* Am J Cardiol, 1995. **76**(3): p. 174-6.
44. Cox, B., M.E. Durieux, and M.A. Marcus, *Toxicity of local anaesthetics.* Best Pract Res Clin Anaesthesiol, 2003. **17**(1): p. 111-36.
45. Mertes, P.M. and M.C. Laxenaire, *Allergic reactions occurring during anaesthesia.* Eur J Anaesthesiol, 2002. **19**(4): p. 240-62.
46. Morcos, S.K., et al., *Prevention of generalized reactions to contrast media: a consensus report and guidelines.* Eur Radiol, 2001. **11**(9): p. 1720-8.
47. Bick, R.L. and E.P. Frenkel, *Clinical aspects of heparin-induced thrombocytopenia and thrombosis and other side effects of heparin therapy.* Clin Appl Thromb Hemost, 1999. **5 Suppl 1**: p. S7-15.
48. Gruchalla, R.S., *10. Drug allergy.* J Allergy Clin Immunol, 2003. **111**(2 Suppl): p. S548-59.
49. Kirchhof, P., et al., *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS.* Europace, 2016. **18**(11): p. 1609-1678.