Evaluation of QDOT MICRO™ catheter for pulmonary vein isolation (PVI) in subjects with Paroxysmal Atrial Fibrillation (PAF)

(Q-fficiency) IDE #G180176

Clinical Study Protocol

Protocol# BWI_2017_07

Version 5.0
February 3, 2021

Sponsor: BIOSENSE WEBSTER, INC.
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1.0 LIST OF ACRONYMS AND ABBREVIATIONS

AAD	Antiarrhythmic drug
ACC	American College of Cardiology
ACT	Activated clotting time
AE	Adverse event
AF	Atrial fibrillation
AFL	Atrial flutter
AHA	American Heart Association
ANOVA	Analysis of variance
AT	Atrial tachycardia
AV	Atrioventricular
BP	Blood pressure
CEC	Clinical Events Committee
CHF	Congestive heart failure
CF	Contact force
CFAE	Complex fractionated atrial electrogram
CHADS	Congestive heart failure, High blood pressure, Age 75+, Diabetes, previous Stroke or transient ischemic attack
CPVI	Complete pulmonary vein isolation
CRF	Case Report Form
CS	Coronary sinus
CT	Computed tomography
CTI	Cavotricuspid isthmus
CVA	Cerebrovascular accident
ECAS	European Cardiac Arrhythmia Society
EPU	External processing unit
ESC	European Society of Cardiology
FDA	Food Drug Administration
GCP	Good Clinical Practice
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
HRS	Heart Rhythm Society
ICD	Implantable cardioverter defibrillator
ICE	Intracardiac echocardiography
ICF	Informed consent form
IEC	Independent Ethics Committee
IFU	Instructions for use
IRB	Institutional Review Board
ITT	Intent-to-treat
HIPAA	Health Insurance Portability and Accountability Act
LA	Left atrium
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MV	Mitral valve
PAF	Paroxysmal atrial fibrillation
PCI	Pecutaneous coronary intervention
PIU	Patient Interface Unit
PP	Per protocol
PV	Pulmonary vein
PVI	Pulmonary vein isolation
QOL	Quality of life
RA	Right atrium
REB	Review Ethics Board
RF	Radiofrequency
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SF	Surround Flow
SVC	Superior vena cava
TIA	Transient ischemic attack
TEE	Transesophageal echocardiogram
TTE	Transthoracic echocardiogram
TTM	Transtelephonic monitoring
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect
VT	Ventricular tachycardia

2.0 KEY ROLES AND RESPONSIBLE PARTIES

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CRO(S) AND CORE LAB(S):
The sponsor maintains a list of CRO(s) and Core Lab(s) and their contact information.

INVESTIGATORS:
The sponsor maintains a list of study Investigators and their contact information.

3.0 STATEMENT OF COMPLIANCE

Study Title: Evaluation of the QDOT MICRO™ Catheter for pulmonary vein isolation (PVI) in subjects with Paroxysmal Atrial Fibrillation (PAF) (Q-fficiency)

Study #: BWI_2017_07

Protocol Type	Revision	Rationale	Effective Date
Original	#1	Original submission	July 17, 2018
Amendment	#2	Changes made in response to the FDA deficiency letter	September 29, 2018
Amendment	#3	Changes made in response to the conditional approval from FDA	November 19, 2018
Amendment	#4	Inclusion of the second study in the clinical study	September 10, 2019
Amendment	#5	Administrative and COVID-19 study assessment updates	February 3, 2021

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)		

4.0 PROTOCOL SUMMARY

Evaluation of QDOT MICRO™ Catheter for pulmonary vein isolation (PVI) in subjects with PAF (QDOT IDE# G180176**)**

Full Title & Protocol Number	Evaluation of QDOT MICRO™ Catheter for pulmonary vein isolation (PVI) in subjects with PAF Protocol #: BWI_2017_07
Short Title	Q-fficiency
IDE/IND number	G180176
Sponsor	CSS/BWI
Indication	Atrial Fibrillation

Study Article Description	• QDOT MICRO™ Catheter (D-1394-XX-SI and D-1395-XX-SI)
	  o Interface Cable (D-1357-03-SI)
	  o Dongle (EM-5050-055F)
	• nMARQ Multi-Channel RF Generator v3.0.1 (D-1341-07I)
	  o v3.0.1 – Main Study
	  o v3.0.6 – Second (Variable Flow) Study
	• CARTO® 3 v6.0.60 QDOT MICRO™ Software Module

Study Design	Prospective, non-randomized, pre-market clinical evaluation of the QDOT MICRO™ Catheter to demonstrate the safety and effectiveness when compared to an historical control performance goal. The trial will have 2 studies: • The Main study includes subjects treated with nMARQ RF generator with constant flow rate (8mL/min) for QMODE+ RF applications. • The Second (variable flow) study will include subjects treated with the nMARQ RF generator with variable flow rate for QMODE+ RF applications. QMODE RF applications will use the same flow rates for both studies. To assess PV stenosis, embedded within the Study will be a Cardiac Computed Tomography (CT) or Magnetic Resonance Angiogram (MRA) image (CT/MRA) subset with consecutive enrollment (n=40). The Main study will enroll 185 subjects who are candidates for catheter ablation. Bayesian adaptive design will be used to assess early success at one interim analysis. The study will be considered successful if primary endpoints are met for Main study. A second (variable flow) study of subjects will enroll 92 subjects who are candidates for catheter ablation. Enrollment for the second study will begin after enrollment for the Main study is complete. The second study will use the same eligibility criteria and the same sites as the Main study. The success of the second (variable flow) study will be based on same endpoints and hypotheses formulated for the main study.

<table>
<tr><td>Sample Size</td><td colspan="2">N = 277 subjects at up to 30 US sites with 185 subjects in the Main study of the study and 92 in the second study.</td></tr>
<tr><td>Study Population</td><td colspan="2">Subjects undergoing electrophysiology mapping and RF ablation for treatment of Antiarrhythmic Drug (AAD) Refractory symptomatic paroxysmal AF with the QDOT MICRO™ catheter.</td></tr>
<tr><td>Geographic areas to be included</td><td colspan="2">Geographic involvement will include the US</td></tr>
<tr><td rowspan="2">Study Duration</td><td colspan="2">~18-20 months (including 6-8 months enrollment and 12 months follow up from LPI) for the Main study
~ 18 months (including 6 months enrollment and 12 months follow up from LPI for Second (variable flow) study.</td></tr>
<tr><td>Start Date: 4Q18</td><td>End Date:4Q21</td></tr>
<tr><td>Procedure(s) Description</td><td colspan="2">
In this study protocol, QMODE+ (90W 4 sec) is the primary temperature control mode for pulmonary vein isolation. If the investigator deems QMODE+ unable to achieve PVI, the study catheter in QMODE temperature control mode (25-50W) should be used to complete the PVI procedure.

In addition, QMODE+ and QMODE (25-50W) are to be used to treat non-PV triggers, Linear ablation lines and the right atrial CTI line when atrial tachycardias are documented during the procedure or by medical history.

QDOT MICRO™ Catheter Parameter Tables:

For the Main study:

Table A: RF and Flow Settings during RF applications
<table>
<tr><th rowspan="2">Power</th><th colspan="2">Target Temp*</th><th colspan="2">Cut-off Temp</th><th rowspan="2">Nominal Irrigation Flow rate</th></tr>
<tr><th>Range</th><th>Maximum allowed</th><th>Range</th><th>Maximum allowed</th></tr>
<tr><td>25-35 W</td><td>40-50ºC</td><td>50ºC</td><td>50-55ºC</td><td>55ºC</td><td>4mL**</td></tr>
<tr><td>36-50W***</td><td>40-50ºC</td><td>50ºC</td><td>50-55ºC</td><td>55ºC</td><td>15mL**</td></tr>
<tr><td>90W†</td><td>40-60ºC</td><td>60ºC</td><td>60-70ºC</td><td>70ºC</td><td>8mL**</td></tr>
</table>
* 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 temp setting for the posterior wall RF applications.

For the Second (variable flow) study:

Table B: RF and Flow Settings during RF applications
<table>
<tr><th rowspan="2">Power</th><th colspan="2">Target Temp*</th><th colspan="2">Cut-off Temp</th><th rowspan="2">Nominal Irrigation Flow rate</th></tr>
<tr><th>Range</th><th>Maximum allowed</th><th>Range</th><th>Maximum allowed</th></tr>
<tr><td>25-35 W</td><td>40-50ºC</td><td>50ºC</td><td>50-55ºC</td><td>55ºC</td><td>4mL**</td></tr>
<tr><td>36-50W***</td><td>40-50ºC</td><td>50ºC</td><td>50-55ºC</td><td>55ºC</td><td>15mL**</td></tr>
<tr><td>90W†</td><td>40-60ºC</td><td>60ºC</td><td>60-70ºC</td><td>70ºC</td><td>4- 15 ml **</td></tr>
</table>
</td></tr>
</table>

	* 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 temp setting for the posterior wall RF applications. **QDOT MICRO™ Ablation:** The QDOT MICRO™ Catheter utilizes a temperature-controlled ablation (QMODE) designed to maximize RF lesion efficiency by using temperature feedback measured at the tip to adjust power and irrigation flow. The QMODE temperature control 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 temperature control mode utilizes changes in the irrigation flow rate as a first-order approach to maintain temperature. If the change in irrigation flow rate is not sufficient, the RF energy is also titrated to maintain temperature. Irrigation Titration for the main study: • For power settings, 35W or lower: The flow rate starts at low flow (4ml, lowest setting). If the temperature approaches or exceeds the set target temperature (50°C), the generator changes the pump flow rate from low (4mL) to high flow (15 mL) to maintain the set maximum power at its setting. Once the temperature decreases the pump irrigation flow rate is returned to low (4mL). • For power settings, greater than 35W: The flow rate starts at high flow (15ml). If the target temperature is not reached, the generator changes the pump from high (15 mL) to low (4mL) flow. Once the temperature increases the pump irrigation flow rate is returned to high (15mL). • For power settings up to 90W: The flow rate starts at moderate flow (8mL) and is maintained throughout the ablation. The duration of the ablation is limited to 4 seconds at this power setting. • At any set power (1-90W), as the tip temperature approaches the selected target temperature (i.e. 50°C) the power level will also titrate down to not exceed the target temperature. If the cut-off temperature is reached, the generator will stop the ablation. Irrigation Titration for the second (variable flow) study: • For power settings, 35W or lower: The flow rate starts at low flow (4ml, lowest setting). If the temperature approaches or exceeds the set target temperature (50°C), the generator changes the pump flow rate from low (4mL) to high flow (15 mL) to maintain the set maximum power at its setting. Once the temperature decreases the pump irrigation flow rate is returned to low (4mL). • For power settings, greater than 35W: The flow rate starts at high flow (15ml). If the target temperature is not reached, the generator changes the pump from high (15 mL) to low (4mL) flow. Once the temperature increases the pump irrigation flow rate is returned to high (15mL). • For power settings up to 90W: The flow rate starts at moderate flow (4mL) and is maintained throughout the ablation. The duration of the ablation is limited to 4 seconds at this power setting. • At any set power (1-90W), as the tip temperature approaches the selected target temperature (i.e. 50°C) the power level will also titrate

	down to not exceed the target temperature. If the cut-off temperature is reached, the generator will stop the ablation Recommendation for CoolFlow® Irrigation Pump Setting and RF Power-delivery • The CoolFlow® Irrigation Pump will deliver a continuous infusion of 2 ml/min of room temperature heparinized saline (1 u heparin/1 ml saline) during mapping. • The nominal irrigation setting will start up to 2 seconds before the onset of RF energy delivery **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 **Post procedure:** 20 minutes waiting period is required followed by adenosine/isoproterenol challenge
Primary Objective	The primary objective of this clinical investigation is to demonstrate the safety and 12-month effectiveness of the QDOT MICRO™ catheter for pulmonary vein isolation (PVI) in the treatment of subjects with paroxysmal atrial fibrillation. Specifically: • To demonstrate the safety based on the proportion of subjects with early-onset (within 7 days of ablation procedure) primary adverse events • To demonstrate the 12-month effectiveness based on the proportion of subject with freedom from documented left atrial arrhythmia (atrial fibrillation (AF), atrial tachycardia (AT) or atrial flutter (AFL)) episodes during the effectiveness evaluation period (Day 91-365)

Secondary Objectives	The major secondary objectives of this study are:
	Safety:
	• to evaluate the incidence of serious adverse events during and after procedure up to 3 months following procedure.
	Acute Effectiveness:
	• Acute Procedural Success as defined by:
	  ○ The % of subjects with electrical isolation of PVs (entrance block) at the end of the procedure, and
	  ▪ The % of subjects with electrical isolation of PVs (entrance block) using QMODE+ as only ablation strategy
	  ▪ The % of subjects with electrical isolation of PVs (entrance block) at all power settings combined
	  ○ The % of subjects with electrical isolation of PVs (entrance block) after waiting period and adenosine challenge

Exploratory Objectives	N/A
Primary Endpoints & Follow-up Intervals	**Acute Safety:** • Incidence of early onset primary adverse events (PAE) related to the device or procedure. Occurrence of Primary AEs within 7 days of an

	ablation procedure. (refer to Appendix A for a comprehensive definition list of primary adverse events) **12-Month Chronic Effectiveness:** • Freedom from documented (Symptomatic and asymptomatic) atrial arrhythmia (atrial fibrillation (AF), atrial tachycardia (AT) or atrial flutter (AFL)) episodes during the effectiveness evaluation period (Day 91-365) **Effectiveness Monitoring:** Effectiveness monitoring will include event Monitoring (TTM). Each subject will be provided an event monitor (Transtelephonic monitor, TTM) no later than at the 3-month visit, episodes ≥ 30 secs on TTM or continuously recorded on the standard 12-leads ECG will be considered recurrence. Subjects will be expected to transmit asymptomatic recordings once every week starting no later than the month 3 visit until the month 6 visit. Starting from month 6, subjects will record and transmit once every month until the end of the 12-month follow-up period. All symptomatic cardiac episodes should be recorded and transmitted soon after the event occurs during the Evaluation Period (Day 91-365).
Secondary Endpoints & Follow-up Intervals	**Secondary Safety Endpoints:** • Incidence of Unanticipated Adverse Device Effects (UADEs) • Incidence of Serious Adverse Events (SAEs) within 7 days (early onset), >7 to 30 days (peri-procedural) and >30 days (late onset) of initial ablation • Incidence of bleeding complication: a) Major, b) clinically relevant non-major and c) minor bleeding as defined in the 2017 HRS/EHRA/ECAS/APHRS /SOLAECE Consensus Statement **Secondary Effectiveness Endpoints:** • Acute Procedural success: o % of subjects with electrical isolation of all PVs (entrance block) at the end of the procedure ▪ The % of subjects with electrical isolation of PVs (entrance block) using QMODE+ as only ablation strategy o % of subjects with electrical isolation of all PVs (entrance block) after first encirclement (evaluated prior to the 20-minute waiting period and adenosine challenge) o % of subjects with electrical isolation of all PVs (entrance block) after first encirclement without acute reconnection, after waiting period and adenosine challenge o % of subjects and % of PVs with touch-up (ablation of acute reconnection) among all targeted veins and touch-up location o Anatomical location of acute PV reconnection after first encirclement • Repeat Ablation Procedures: o Incidence (%) of repeat ablation procedures during 12-months period post-procedure o % PVs re-isolated among all of the targeted PVs at repeat procedure o % repeat ablation procedures requiring new linear lesions and/or identifying new foci outside of initially isolated area among the

	repeat ablation procedures • 12-Month Single Procedure Success o The 12-month single procedure success is defined as freedom from documented AF/AFL/AT recurrence (episodes ≥ 30 secs) during the Evaluation Period after a single ablation procedure and off AADs. Any repeat ablation procedure or AAD therapy will be deemed effectiveness failure for this analysis **Additional Endpoints:** • Procedural data o total procedure time, PVI time, RF application time, mapping time, and RF application time per lesion o fluoroscopy time/dose o location of RF applications, number of RF applications o RF ablation parameters per application o Total fluid/irrigation delivered o Esophageal monitoring o VISITAG™ parameters will be collected in the CARTO® 3 system during the ablation procedures for generation of LA ablation maps o VISITAG SURPOINT™ values (Tag Index) per RF application • Quality of Life (QOL) status (AFEQT scores) • Cardiac CT/MRA Subset for PV Stenosis Assessment • HEMA o Incidence of hospitalizations post-index ablation procedure
Inclusion Criteria	Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1. Symptomatic paroxysmal AF with one electrocardiographically documented AF episode within 6 months prior to enrollment ,a physician's note indicating recurrent self-terminating AF within 7 days. Documentation may include electrocardiogram (ECG); Transtelephonic monitoring (TTM), Holter monitor or telemetry strip. 2. Failed at least one (1) antiarrhythmic drug (AAD) (class I or III) as evidenced by recurrent symptomatic AF, contraindicated or intolerable to the AAD. 3. Age 18 years or older. 4. Signed Patient Informed Consent Form (ICF). 5. Able and willing to comply with all pre-, post-, and follow-up testing and requirements.
Exclusion Criteria	Subjects who meet any of the following exclusion criteria are not eligible for enrollment. 1. Previous surgical or catheter ablation for atrial fibrillation. 2. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause. 3. Patient on amiodarone at any time during the past 3 months prior to enrollment.

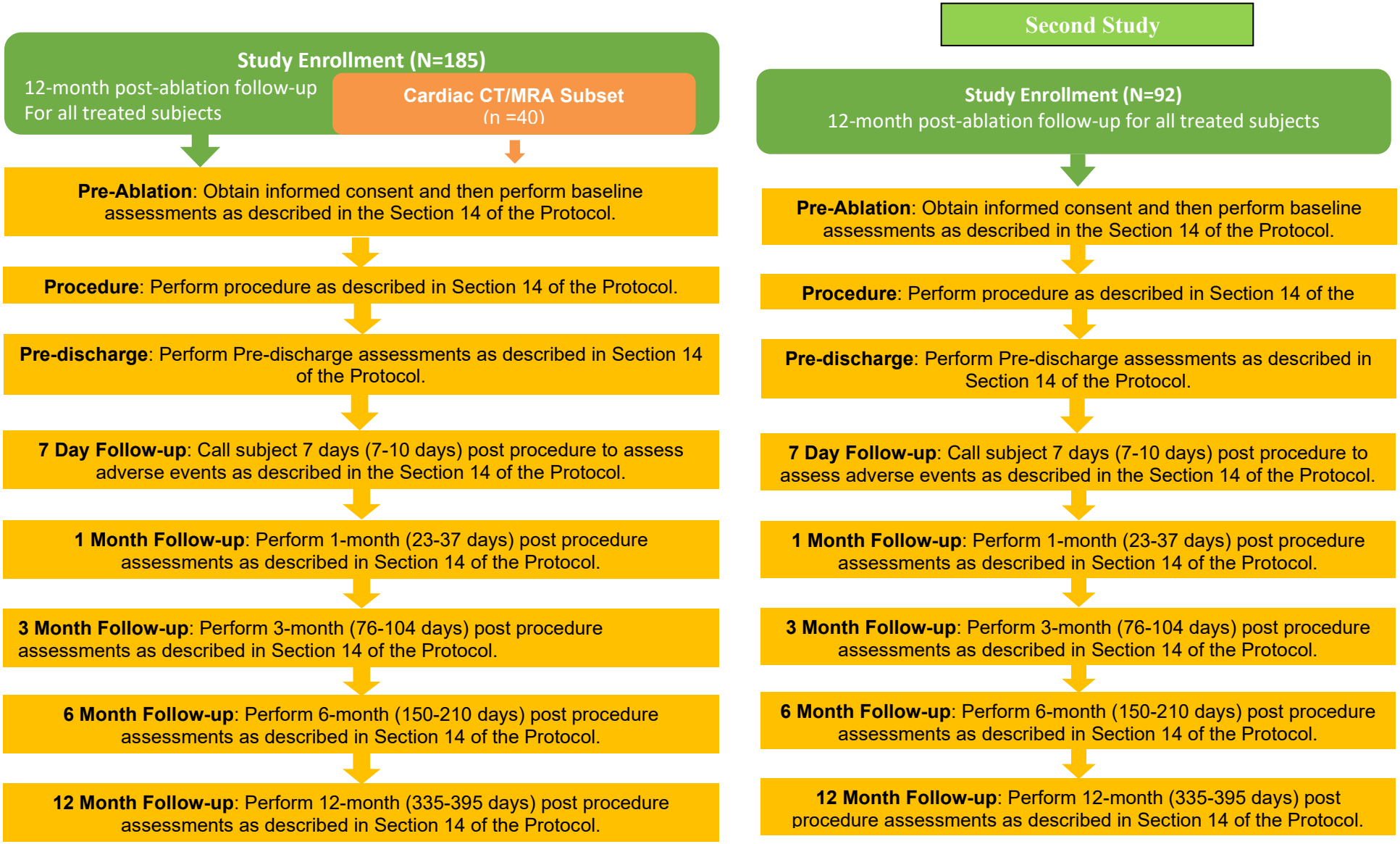
	4. Previously diagnosed with persistent or long-standing persistent AF and/or Continuous AF lasting > 7 days 5. CABG surgery within the past 6 months (180 days). 6. Valvular cardiac surgical/percutaneous procedure (i.e., ventriculotomy, atriotomy, and valve repair or replacement and presence of a prosthetic valve). 7. Any carotid stenting or endarterectomy within the last 6 months. 8. Documented LA thrombus on imaging (within 48 hr prior of a study ablation procedure). 9. Documented LA size > 50 mm (parasternal long axis view). 10. Documented LVEF < 40%. 11. Contraindication to anticoagulation (e.g. heparin) 12. History of blood clotting or bleeding abnormalities 13. MI/PCI within the past 2 months (60 days) 14. Documented thromboembolic event (including TIA) within the past 12 months (365 days) 15. Rheumatic Heart Disease 16. Uncontrolled heart failure or NYHA function class III or IV 17. Severe mitral regurgitation (Regurgitant volume ≥ 60 mL/beat, Regurgitant fraction ≥ 50%, and/or Effective regurgitant orifice area ≥ 0.40cm^2) 18. Awaiting cardiac transplantation or other major cardiac surgery within the next 12 months (365 days) 19. Unstable angina 20. active systemic infection or sepsis 21. Diagnosed atrial myxoma or presence of an interatrial baffle or patch. 22. Presence of implanted ICD/CRT-D. 23. Significant pulmonary disease, (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces chronic symptoms. 24. Severe Gastroesophageal Reflux Disease (GERD; active requiring significant intervention not including OTC medication) 25. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study. 26. 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 study 27. Enrollment in an investigational study evaluating another device, biologic, or drug. 28. Presence of intramural thrombus, tumor or other abnormality that precludes vascular access, or manipulation of the catheter.

	29. Presence of an inferior vena cava filter. 30. Presenting contra-indication for the devices (e.g. TTE, CT, etc.) used in the study, as indicated in the respective instructions for use. 31. Life expectancy less than 12 months
Statistical Analysis	**<u>For the Main study:</u>** **Primary Safety Endpoint** Sample Size and Power Calculations • Based on a performance goal of 14%, an anticipated rate of 7% for the primary safety endpoint, approximately 185 evaluable subjects will provide at least 80% power to declare success for the primary safety endpoint in the main study controlling one-sided alpha of 2.5%, assuming a 5% attrition rate. **Primary Effectiveness Endpoint** Sample Size and Power Calculations • Based on a performance goal of 50%, and anticipated freedom from AF/AT/AFL recurrence rate of 65%, approximately 185 evaluable subjects will be required to obtain at least 80% power to declare success for primary effectiveness endpoint in the main study controlling one-sided alpha of 2.5%, assuming a 12% attrition rate. The Final analyses for primary safety and effectiveness endpoints will apply Bayesian methods and use a beta-binomial model (assuming early success is not achieved for the primary effectiveness endpoint). **For the Variable flow study:** **Primary Safety Endpoint** Sample Size and Power Calculations • Based on a performance goal of 14%, an anticipated rate of 7% for the primary safety endpoint, with borrowing up to 91 subjects from the main study, the sample size of 92 subjects, will provide close to 80% power for testing the primary safety endpoint controlling one-sided alpha of 2.5%, assuming a 5% attrition rate in the variable flow study. **Primary Effectiveness Endpoint** Sample Size and Power Calculations • Based on a performance goal of 50%, and anticipated freedom from AF/AT/AFL recurrence rate of 65%, with borrowing up to 91 subjects from the main study, the sample size of 92 subjects will be required to obtain at least 80% power to achieve success for primary effectiveness endpoint controlling one-sided alpha of 2.5%, assuming a 12% attrition rate in the variable flow study. The analyses for primary safety and effectiveness endpoints will apply Bayesian methods and use a beta-binomial with data borrowing from the Main study using a propensity score-integrated power prior approach.
Interim Analysis	One early success claim interim analysis will be executed for main study
Determination if DMC/CEC required	CEC will be convened to adjudicate the primary safety endpoint. Data Monitoring Committee (DMC) will be responsible for reviewing the study results. The same committees will be responsible for both studies.

Time and Events Schedule	Subjects will be evaluated prior to the procedure, prior to discharge, and post procedure at 7 days (7-10 days), 1 month (23-37 days), 3 months (76-104 days), 6 months (150-210 days), and 12 months (335-395 days) unless otherwise specified in the protocol. • Baseline o Demographics o Medical History ▪ AAD Medication History ▪ Arrhythmia History o Quality of Life Assessment ▪ Quality of Life – Atrial Fibrillation Effect on Quality of life (AFEQT) o Device Interrogation (if applicable) o TTE or TEE evaluation • Ablation Procedure o Ablation procedure strategy outside of the pulmonary vein ostia will utilize QMODE +/ QMODE and Investigator's Standard of Care Data Collection: o Catheter Information (Serial #, Lot #) o Dongle (Serial #) o RF Generator Information (Serial #) o Target sites for RF lesion application ▪ Target Sites ▪ Number of RF Applications per target ▪ total RF duration per application (sec) ▪ Fluoroscopy time/dose ▪ Esophageal temperature monitoring ▪ ICE usage, if used ▪ Procedure Times - Total procedure time - Total mapping time - Total RF time - Time to PVI ▪ Fluid delivered - From the Study Catheter - From IV (if applicable) o CARTO and modified RF Generator download for offline analysis ▪ Segmentation of LA ablation maps based on chosen CARTO tags ▪ Full Case backup [including complete VISITAG export] and CARTO Case recording ▪ RF Ablation parameters per application: Power, Impedance, Flow Rate, Temperature, and Time ▪ Contact force measurements and RF ablation parameters ▪ VISITAG SURPOINT™ value per application, if used ▪ Localized ECG Electrodes measurements for offline analysis o Acute Success (entrance and exit block PVI) o Adverse Events o Cardiac medications • Discharge o Recurrence of arrhythmia prior to discharge o Device Interrogation (if applicable)

	○ HEMA Billing information ○ Adverse Events • Follow-up Assessments Post Ablation* ○ 7 Day phone Call ○ 1-month ○ 3-month ○ 6-month ○ 12-month Data to be collected during the study visits will include: • Adverse Events (since last visit) • Physical Exam • Medication update/changes • Quality of Life Assessment (at 3-, 6-, and 12-month visit) ○ Quality of Life – Atrial Fibrillation Effect on QualiTy of life (AFEQT) • Billing Information for all hospitalizations, ER visits and outpatient visits for economic analyses • ECG • Recurrence of Study Arrhythmia (each patient will be provided a TTM event monitor) • Repeat ablation procedures/subject during the follow-up period, repeat ablation procedure will be at the discretion of the investigator • Throughout the 12-month effectiveness follow-up period, arrhythmia status will be assessed by symptom-initiated event monitoring. ▪ Device Interrogation (if applicable) ▪ All symptomatic cardiac episodes will be documented *based on the initial ablation procedure
QUALIFICATION AND ACTIVATION OF OPERATORS	• Experience with Focal Catheters and AF ablation ≥100 cases • Operators – Investigator training is required for the Protocol and Investigational QDOT MICRO™ Catheter

5.0 SCHEMATIC OF STUDY DESIGN



Evaluation of QDOT MICRO™ catheter for pulmonary vein isolation (PVI) in subjects with Paroxysmal Atrial Fibrillation (PAF)

6.0 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

6.1 Background

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.[1, 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."[4] Creation of transmural, continuous, and durable RF lesions is the objective of PVI. Conventional parameters of radiofrequency (RF) ablation with irrigated catheters involves 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%.[9, 10] 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.[11, 12]

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.[13]

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.[14, 15] This can be achieved by delivering a large current for a short duration.

6.2 Previous Experience with the QDOT MICRO™ Catheter and nMARQ RF Generator

6.2.1 QMODE Animal Testing

6.2.1.1 QMODE with the QDOT MICRO™ Catheter Thigh Prep

Animal testing was performed using the catheter and complete system per study protocol P-0022114 and test report TR-0022114, Verification of QDOT Micro-Electrode Catheter with Q-mode Ablation Mode – Canine Thigh Preparation Test.

Purpose:

The purpose of this study was to evaluate the safety and performance of the QDOT MICRO™ electrode catheter using QMODE ablation mode (Test Catheter) when compared with STSF and ST catheters using power control mode (Control catheters) using a well-established canine thigh muscle model.

Scope:

The QDOT MICRO™ catheter is intended to be used clinically thus the primarily focus of this test was to assess the safety and performance of QDOT MICRO™ electrode catheter using QMODE ablation mode. The following objectives were tested:

- Char/coagulum and steam pop rate of QDOT MICRO™ catheter using QMODE ablation mode compared with STSF and ST catheters using power control mode.
- Lesion dimensions (max depth, max diameter and surface diameter) comparison between test and control catheters.
- Ablation parameters were collected for analysis for characterization purposes to understand the similarities and differences in their behavior when compared to control catheters: average power, maximum electrode temperature, Temperature Rise, Initial Impedance, Impedance Drop.

Summary:

The overall incidence of coagulum observed with the QDOT MICRO™ catheter in QMODE ablation mode was similar to STSF (Control Catheter) and significantly less compared to the ST (Control catheter). The overall incidence of Steam pops observed with the QDOT MICRO™ catheter in QMODE ablation mode was similar compared to the STSF and ST (Control catheters). The lesion characteristics were similar between the QDOT MICRO™ catheter and the control catheters. The overall performance of the QDOT MICRO™ catheter, in the QMODE ablation mode was similar or better compared to the control catheters (ST and STSF) in power control ablation mode.

Conclusions:

Based on the results of the canine thigh prep study, the overall safety and performance (Coagulum, Steam pops) of the QDOT MICRO™ catheter, when used in the QMODE ablation mode, is similar compared to the control catheters (STSF, ST) being used in power control mode. The maximum ablation parameters identified for the QDOT

MICRO™ catheter, in the QMODE ablation mode have been tested and assessed to be safe and effective based on the results of this canine thigh prep study.

6.2.1.2 QMODE with the QDOT MICRO™ Catheter In Vivo Animal Testing

Animal testing was performed using the catheter and complete system per study protocol P-0023068 and test report TR-0023068, Evaluation of QDOT MICRO-Electrode Catheter with Q-mode Ablation Mode - Beating Heart Animal Study.

Purpose:

The purpose of this acute study was to evaluate the safety and overall functional performance of the QDOT MICRO™ electrode catheter, in the QMODE ablation mode (nMARQ multichannel RF generator), when simulating a clinical pulmonary vein isolation (PVI) procedure. The overall safety and functional performance of the QDOT MICRO™ electrode catheter and QMODE ablation mode was compared to the control catheter (Smart Touch SF) being used in power control mode (Smart Ablate generator).

Discussion:

The QMODE Beating Heart study was conducted according to the study protocol design and its requirements.

No char/coagulum observed on the test catheter (QDOT MICRO™). The overall incidence of steam pop observed with QDOT MICRO™ (0 in RA, 5/9 in the LV and 0 in all other locations) was lower compared to the control STSF catheter (0 in RA, 3/36 during PVI, 5/12 in LA wall, 5/6 in LV and 1/7 in RV). Of note, there were zero incidence of steam pop occurrence in both left and right atrial ablations using QDOT MICRO™ catheter with QMODE at the study settings.

The QDOT MICRO™ ablation catheter used in conjunction with the QMODE ablation mode was able to:

- Deliver RF energy at a target site
- Demonstrate acute isolation of the pulmonary vein.
- Demonstrate clinically acceptable signal quality which was comparable to control.
- Pace from ring electrodes and microelectrodes during idle-state and during ablation.
- Provide significantly better temperature feedback during ablation than control catheter.
- Function effectively when used in conjunction with ancillary equipment like nMARQ multichannel RF generator, QDOT Dongle, CoolFlow pump and CARTO 3 mapping system.

The QDOT MICRO™ ablation catheter, when used with QMODE ablation mode, was able to produce effective electrogram signal attenuation and equivalent to (or better) lesions as compared to that with the STSF catheter in all four cardiac chambers.

The nMARQ generator was able to successfully modify the irrigation flow rate based on QDOT MICRO™ catheter electrode temperature response and power settings to maintain temperature limit when used in the QMODE ablation mode.

Conclusions:

The QDOT MICRO™ ablation catheter with QMODE ablation mode using the temperature target and flow rate settings as set forth by the protocol, meets all acceptance criteria as listed in protocol P-0023068.

The overall functionality and the safety of the QDOT MICRO™ ablation catheter with QMODE ablation mode is equivalent to or better than that of the control STSF catheter.

6.2.2 QMODE+ Mode with the QDOT MICRO™ Catheter Animal Testing

6.2.2.1 QMODE+ Mode with the QDOT MICRO™ Catheter Thigh Prep

Animal testing was performed using the catheter and complete system per study protocol P-0022211 and test report TR-0022211, Verification of QDOT Micro-Electrode Catheter with QMODE+ Ablation Mode – Canine Thigh Preparation Tests.

Purpose:

The purpose of this study was to evaluate the safety and performance of the QDOT MICRO™ Catheter in QMODE+ (high power, short duration) ablation mode (90W/4s) using the nMARQ Multi-channel RF generator. The overall safety and performance of the QDOT MICRO™ catheter in the QMODE+ ablation mode was compared to the safety and performance of STSF catheter (Control catheter) in power control mode at two different settings (50W/10s or 30W/30s) using the Smart Ablate RF generator, using a well-established canine thigh muscle model.

Scope:

The QDOT MICRO™ catheter is intended to be used clinically thus the primarily focus of this test was to assess the safety and performance of QDOT MICRO™ electrode catheter using QMODE+ ablation mode. The following objectives were tested:

- Safety of QDOT MICRO™ catheter using QMODE+ ablation mode (char/coagulum and steam pop) compared with STSF catheter using power control mode.
- Lesion dimensions (max depth, max diameter and surface diameter) comparison between test and control catheters.
- The following ablation parameters were collected for analysis for characterization purposes only (no acceptance criteria) in order to understand the similarities and differences in their behavior when compared to control catheter: average power, maximum electrode temperature, Temperature Rise, Initial Impedance, Impedance Drop.

Summary:

There was no significant difference in the overall incidence of coagulum observed with the QDOT MICRO™ catheter in QMODE+ ablation mode compared to the STSF

(Control Catheter) in power control mode, when tested in both perpendicular and parallel orientations. A small Grade 1 (Grade 1: ≤1mm3) was observed with the Qdot catheter at 90W/4s with perpendicular orientation at 30g. Whereas one Grade 1(Grade 1: ≤1mm3) observed with STSF catheter at 50W/10s with parallel orientation at 10g and one Grade 2 (Grade 2:>1mm3) was observed at 30W/30s with parallel orientation at 30g.

No Steam pop was observed with the QDOT MICRO™ catheter in QMODE+ ablation mode in Perpendicular as well as Parallel orientation at 10g and 30g. One steam pop was observed with STSF catheter (Control Catheter) at 50W/10s with perpendicular orientation at 30g and two steam pops were observed at 30W/30s with parallel orientation at 30g.

The lesion depth was significantly smaller with the QDOT MICRO™ in QMODE+ ablation mode than the STSF catheter in Power control mode for both perpendicular and parallel with 10g and 30g. The lesion diameter was greatest with the STSF catheter in power control mode for 30W/30s for both perpendicular and parallel orientation at 10g and 30g. However, lesion diameter of QDOT MICRO™ catheter in QMODE+ ablation mode (90W/4s) and STSF (50W/10s) in power control mode was similar. The overall safety of the QDOT MICRO™ catheter, in the QMODE+ ablation mode was similar or better compared to the control catheter (STSF) in power control ablation mode.

Conclusion:

Based on the results of the canine thigh prep study, the maximum ablation parameters identified for the QDOT MICRO™ catheter, in the QMODE+ ablation mode have been tested and assessed to be safe and effective.

6.2.2.2 QMODE+ Mode with the QDOT MICRO™ Catheter In Vivo Animal Testing

Animal testing was performed using the catheter and complete system per study protocol P-0022212 and test report TR-0022212, Acute Canine Beating Heart Study for Validation of QMODE+ with QDOT MICRO™ Catheter.

Purpose:

The purpose of this study was to verify safety and effectiveness of the QDOT MICRO™ catheter using the QMODE+ mode (test group) as compared to the STSF catheter using the power control mode (control group) in a simulated clinical environment using the canine beating heart model.

Scope:

The test focused on the safety and effectiveness of the QDOT MICRO™ catheter with QMODE+ mode as compared with the STSF catheter using power control mode.

- QMODE+ primary safety endpoints
    - Char, Coagulum and Steam pop
    - Primary adverse event: cardiac perforation, tamponade and death
    - Collateral damage in the heart and adjacent organ/tissues

- QMODE+ secondary effectiveness endpoints
    - Endocardial and epicardial surface diameters
    - Lesion depth and transmurality and PVI rate
    - Signal quality (M1-4 compared to control, μ1-3 qualitive measurements)

Discussion:

The QMODE+ Beating Heart study was conducted according to the study protocol design and its requirements.

No char/coagulum observed on the test catheter (QDOT MICRO™). The overall incidence of steam pop observed with QDOT MICRO™ (0 in all locations) was lower compared to the control STSF catheter (1 in LA PVI). Of note, there were zero incidence of steam pop occurrence in the right atrial location and both the left and right ventricular locations using QDOT MICRO™ catheter with QMODE+ at the study settings.

The QDOT MICRO™ ablation catheter used in conjunction with the QMODE+ mode was able to:

- Deliver RF energy at a target site
- Demonstrate acute isolation of the pulmonary vein.
- Demonstrate clinically acceptable signal quality which was comparable to control.
- Pace from ring electrodes and microelectrodes during idle-state and during ablation.
- Provide significantly better temperature feedback during ablation than control catheter.
- Function effectively when used in conjunction with ancillary equipment like nMARQ multichannel RF generator, QDOT MICRO Dongle, CoolFlow pump, and CARTO 3 mapping system.

The QDOT MICRO™ ablation catheter, when used with QMODE+ mode, was able to produce effective electrogram signal attenuation with equivalent (or better) lesions as compared to those with the STSF catheter in all four cardiac chambers.

Conclusions:

The QDOT MICRO™ ablation catheter with QMODE+ ablation mode using the temperature target and flow rate settings as set forth by the protocol, meets all acceptance criteria as listed in protocol P-0022212.

The overall functionality and the safety of the QDOT MICRO™ ablation catheter with QMODE+ mode is equivalent to or better than that of the control STSF catheter.

6.2.3 QDOT MICRO GLP Study

Purpose:

This study was designed to evaluate overall safety of a new modified therapeutic micro-electrode ablation catheter (QDOT MICRO™) and demonstrated that added catheter features do not introduce any new safety risks when compared to its predicate device Biosense Webster THERMOCOOL SMARTTOUCH® SF catheter.

Results:

Overall, The GLP study findings met all endpoints concerning the safety of the Test catheter:

- Occurrence of thrombus and/or charring on the catheter tip:

There was no evidence of thrombus and/or charring on any of the catheters used and examined, following delivery of RF energy.

- Occurrence of mural thrombus in the treated heart chambers:

There was no evidence of mural thrombus detected during the ablation or follow-up procedures using intracardiac echo or at the treatment sites that could be detected macroscopically or microscopically.

- Pulmonary vein stenosis:

There was no evidence of pulmonary vein stenosis in any of the animals regardless of treatment or group assignment.

- Occurrence of collateral damage:

Collateral damage to the adjacent tissues was rare, was occasionally observed at the hilus in the right lung lobes and in the pulmonary artery and aorta. These lesions were self-limited, did not disrupt the integrity of tissues involved and showed optimal healing through fibrosis.

- Occurrence of device related mechanical injury:

There was no pathologically meaningful procedural trauma in any of the treated sites with rare exceptions of minor endocardial tears that were fully healed at 30 days with no evidence of prior thrombosis.

- Occurrence of peripheral thrombo-emboli:

No thrombo-emboli or ischemic lesions were observed in downstream tissues: brain, myocardium, kidneys, liver, spleen and lungs based on screening through systematic bread-loafing with gross evaluation and systemic sampling for microscopic evaluation.

Overall, The GLP study findings met all endpoints concerning efficacy of the Test catheter:

- Effectiveness of ablation in the left atrium

Elimination of PV electrical potential could be confirmed immediately following ablations in all animals regardless of group assignment or treatment received. In addition, this study demonstrated long term effectiveness of pulmonary vein isolation using the Test or Control catheters as delayed conduction (only in Animal 1244, Group 2) or no electrical potential could be detected in the treated pulmonary veins at 35-36 days post isolation.

- Effectiveness of ablation in the right atrium

All ablations delivered to the right atrium regardless of ablation settings or ablation catheter use were found effective as a greater than 50% reduction in the electrogram amplitude.

Conclusions:

Biosense Webster QDOT MICRO™ ablation catheter met the safety and efficacy criteria set forth in the study protocol when used with nMARQ™ RF generator, Carto 3 EP navigation system, CoolFlow irrigation pump, catheter interface cable, and standard pacing system for ablation in the beating heart of a chronic canine model without any significant device related clinical adverse events.

In conclusion, this study demonstrated that added catheter features do not introduce any new safety risks when compared to its predicate device Biosense Webster THERMOCOOL SMARTTOUCH® SF catheter.

6.2.4 QDOT FIM Studies

Two feasibility studies are underway to assess the performance of the QDOT Micro™ Catheter.

6.2.4.1 QDOT MICRO™ Workflow

The purpose of QDOT MICRO™ Workflow study is to evaluate the workflow and acute performance, during standard electrophysiology mapping and RF ablation procedures, of the QDOT MICRO™ catheter. This study is a prospective, multi-center, non-randomized, interventional clinical study. The target population are paroxysmal AF subjects who are scheduled to undergo a clinically-indicated ablation procedure for management of their paroxysmal AF. Subjects will be followed up at 7 days and 3-month post-procedure.

The main objectives of the study are acute device performance and acute safety. The study will enroll 50 subjects at 5 centers in Europe.

6.2.4.2 QDOT MICRO™ QMODE+ FIM

The purpose of this feasibility study is 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 a prospective, multi-center, non-randomized, interventional clinical study. 50 paroxysmal AF subjects who are scheduled to undergo a clinically-indicated ablation procedure for management of their paroxysmal AF will be enrolled at up to 10 centers in Europe. The subjects will be followed till 3-months post-procedure.

6.3 Rationale

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.

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 this study protocol (refer to Sections 6.2.2 and 6.2.3).

Delivery of high RF power for short duration (90W, 4 seconds) achieves uniform transmural lesions, mainly relying on resistive heating [16-19] QMODE+ at up to 90W, 4 seconds may significantly shorten RF ablation time while maintaining the effectiveness and safety profile. A temperature limit has been defined 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.

6.3.1 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 7.3.1a), 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.

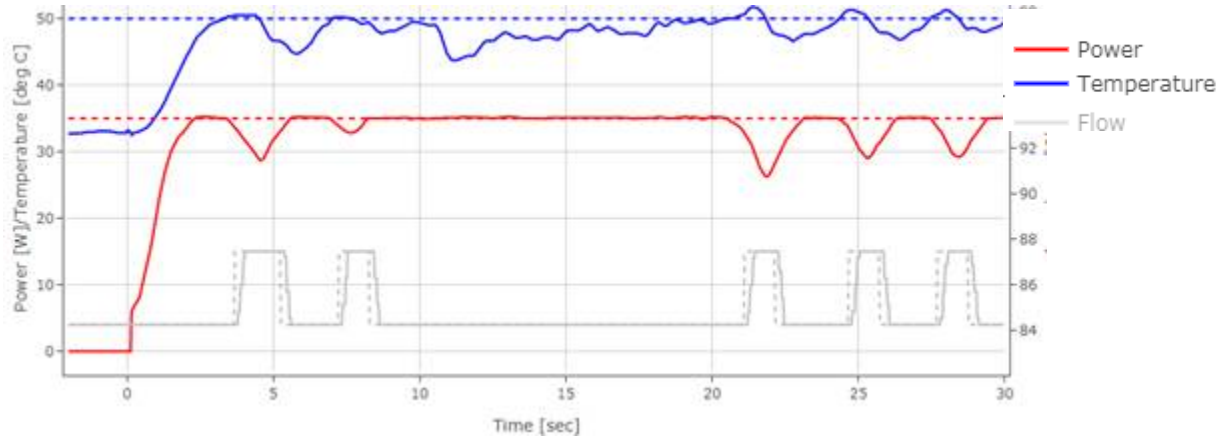
In a second example (see Figure 7.3.1b), the power delivery (e.g. 50W) starts with the irrigation setting at 15 ml/min until it reaches a target temperature (e.g. 50°C). If the catheter is below the desired temperature initially, the irrigation is automatically reduced to 4ml/min by the generator algorithm 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.

Main Study

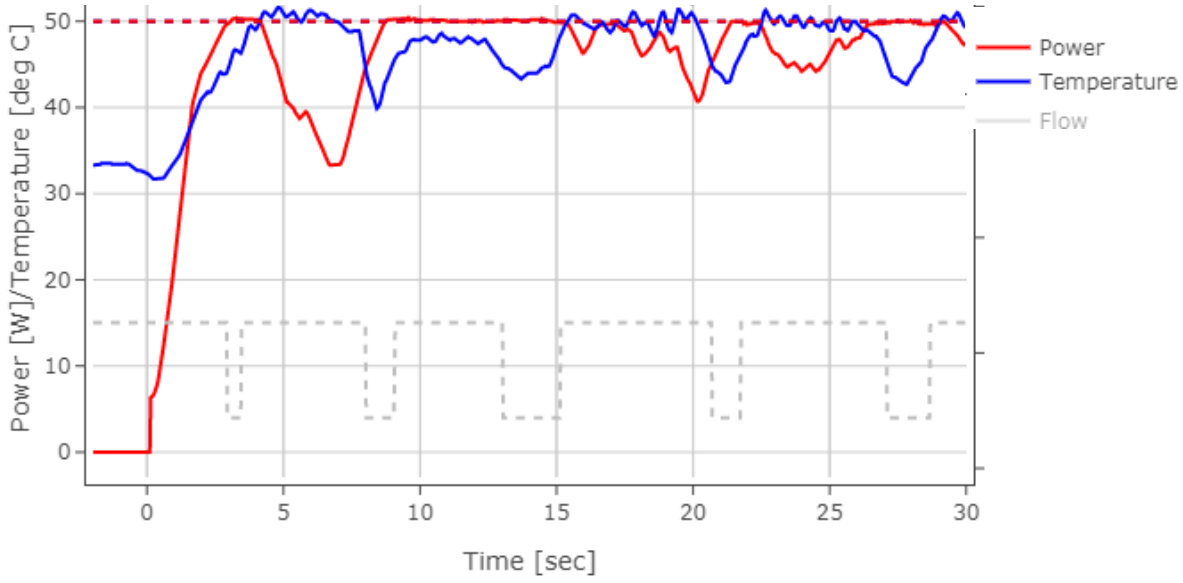
For power settings at 90W (Figures 6.3.1C and 6.3.1D), the maximum duration is set to 4 seconds. Therefore, the approach is to only titrate power. At this setting, power delivery is delivered at a constant irrigation flow of 8 ml/min with no modulation given the short duration.

Figure 6.3.1A-D: Graphs of the Generator Power over Time

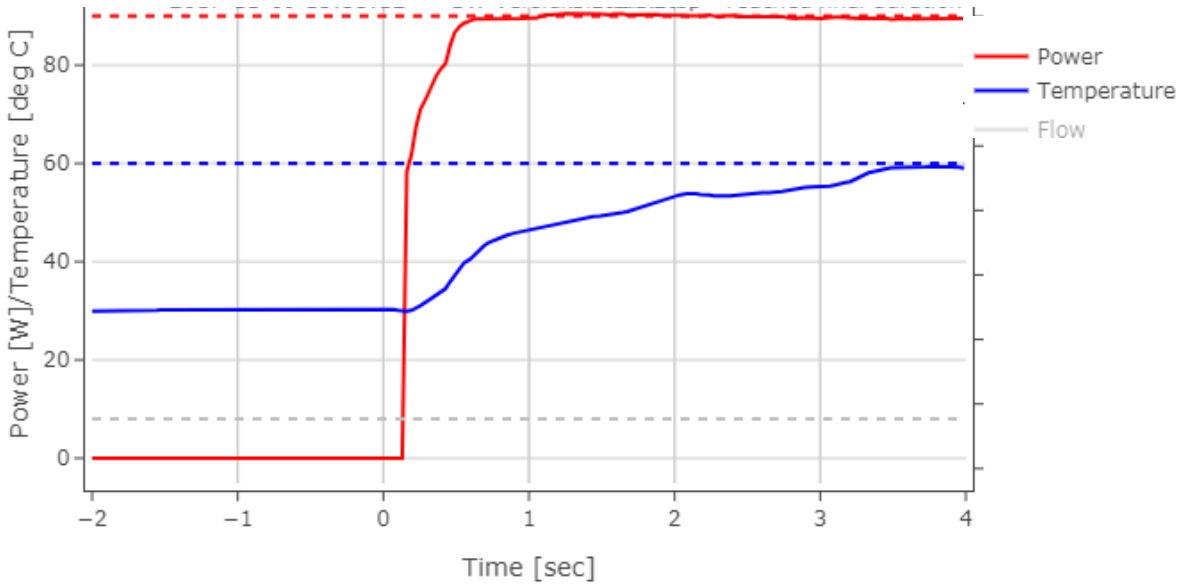
A. RF Power Delivery at 35W



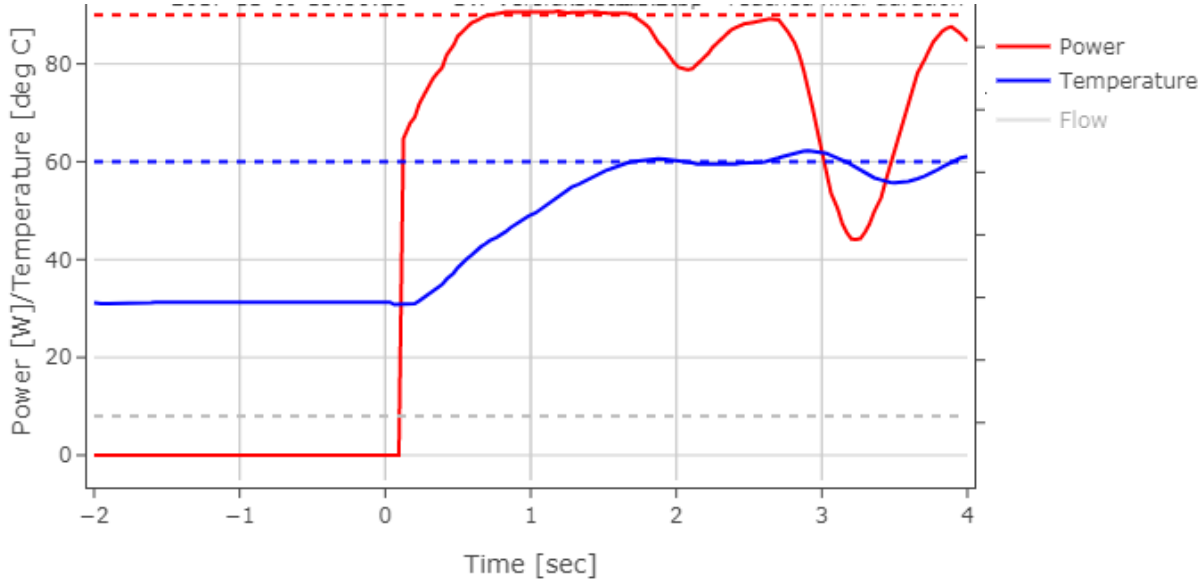
B. RF Power Delivery at 50W



C. RF Power Delivery at 90W



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



Second (Variable Flow) Study

RF energy modulation for Variable Flow rate:

The QDOT MICRO catheter is designed to work in a temperature control/power and irrigation modulation mode. This is how the system works for QMODE (refer to Figures 6.3.1A and Figure 6.3.1B above). However, when making 90W RF applications with a constant irrigation flow (8 mL/min) the system only worked in power control mode.

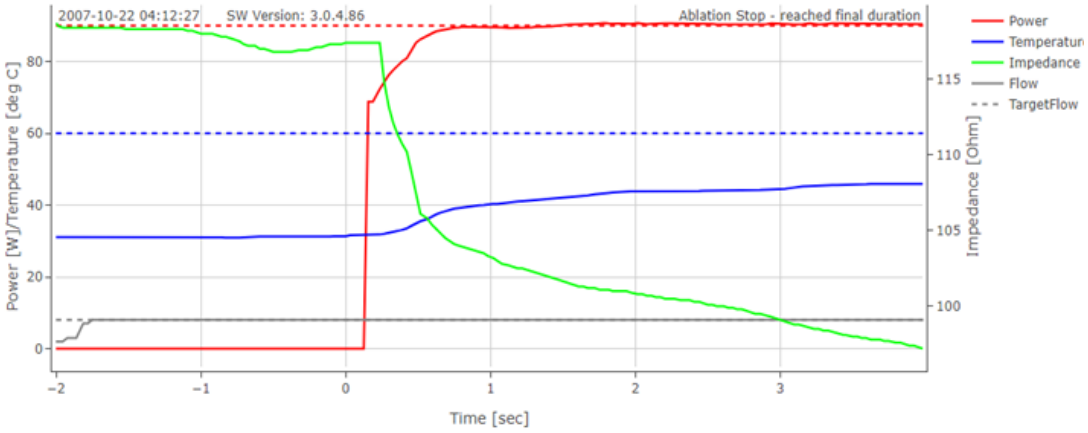
The purpose of the variable flow irrigation option is to improve the catheter tip temperature response during high power, short duration (Qmode+) ablations. This is

achieved by optimizing the flow rate (4-15 mL/min), which minimizes the impact of constant irrigation (8 mL/min) on the lack of catheter tip temperature response during short duration (4s) 90W RF applications (refer to Figure 6.3.2A and Figure 6.3.2B).

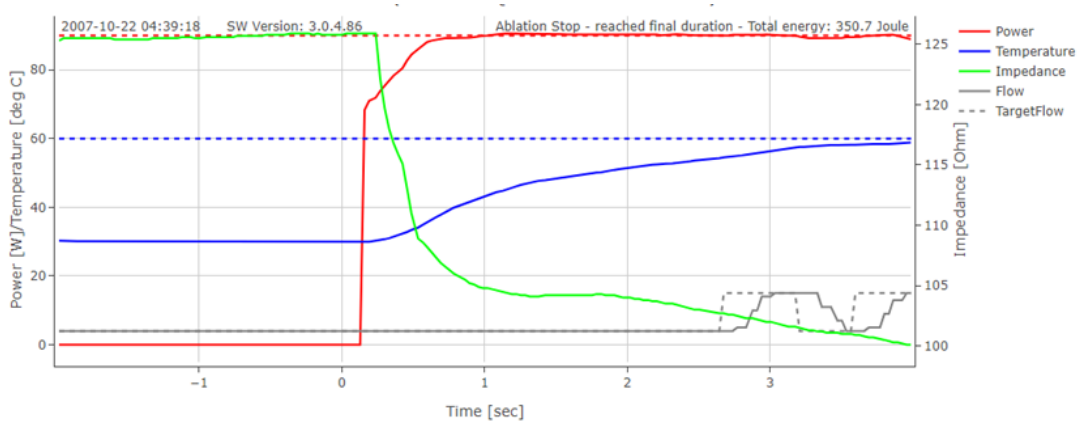
For power settings at 90W (Figures 6.3.2A and 6.3.2B), the maximum duration is set to 4 seconds. Therefore, the approach is to only titrate power. At this setting, power delivery is delivered with a variable flow rate. Irrigation at 4 mL/min starts with the initiation of 90W energy application. The flow rate remains at 4 mL/min if the catheter tip temperature remains below the target energy cutoff temperature (refer to Figure 6.3.2A). If the catheter tip 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 (refer to Figure 6.3.2B).

Figure 6.3.2A-B: Graphs of the Generator Power over Time

A. Example 1 at 90W: Temperature does not approach Target Temperature (flow rate 4mL/min)



B. Example 2 at 90W: Temperature approaches Target Temperature (flow rate changes to 15 mL/min)



6.4 Potential Risk and Benefit

After over two decades of intracardiac radiofrequency (RF) catheter ablation, the procedural risks and complications associated with routine RF ablation are well documented and understood. Procedural risks posed by the QDOT MICRO™ catheter are expected to be comparable to these known anticipated risks.[3, 4, 20]. 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:

6.4.1 Description and Analysis of Risks

Risks associated with catheter ablation

Studies have reported low rates of major complications (0.8%)[21, 22] with major centers worldwide reporting rates lower that <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)[4], 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%[25]. Rates as low as 0.18% have also been reported in a recent study that reviewed complications among 2,750 procedures[22].

The general incidence of pericardial effusion during AF ablation is around 1.2% to 1.3%[21, 23]. Cardiac perforation may result from catheter manipulation or application of radiofrequency current. Published risks of cardiac perforation range from <1%to 2.4%[23]. However the risk of perforation is decreased with advances in catheter technology[26]. 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[27]. 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% [28] that rarely may progresses to an atrial esophageal fistula (AEF) with catastrophic consequences[29]. Esophageal injury by endoscopy has a prevalence between 2.2 to 21%[28]. Esophageal perforation is a dreaded complication of atrial fibrillation ablation that occurs in 0.02 to

11% [28, 30] 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 supposed to be around 0.1% of the procedures[31]. Studies using luminal temperature monitoring to identify potentially dangerous heating of the esophagus during ablation have not been able to demonstrate reduction in incidence[32].

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 [4, 32, 33]. A 2018 published study reported very low rates of PNP of 0.04% among 2,750 procedures[22]. 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%[4]. 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%)[34, 35]. Among the most frequent causes of death were cardiac tamponade (25% of deaths), stroke (16%), atrio-esophageal fistula (16%) and massive pneumonia (6%)[35].

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[36]. Experience at numerous centers suggests that the risk of coronary occlusion is less than 0.5%[37]. 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%[23]. More recently, Fuji et al have reported

incidence of thromboembolism up to 5% of patients undergoing AF ablation despite perioperative anticoagulation[38]. 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[39].

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[40]. 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%)[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%).[4, 43, 44] 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%).[45-47]

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%).[48-52]

Infection: The percutaneous procedure carries risk of infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk < 0.5%).[43, 44] 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.

Investigational device related risks

A review of the testing of the investigational devices verifies that risks associated with the designs are acceptable and no 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 investigational devices 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 investigational devices when used in accordance with the Instructions for Use.

Biocompatibility and Sterility Assessments for the applicable investigational devices 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 investigational devices has verified that there are no "Intolerable" ratings related to risks associated with the designs of the devices. All ratings are "As Low As Practical" (ALAP).

6.4.2 Minimization of Risks

Appropriate measures have been outlined in the study protocol to minimize the risk to subjects, while still providing the possible benefits of the treatment options to be studied. 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. Additionally, the risk of potential adverse events is mitigated by the temp cutoff setting of the generator and the optimization of the target temperature.

Subjects will be screened carefully prior to enrollment in the study to ensure compliance with the inclusion and exclusion criteria. The exclusion criteria have been developed to eliminate confounding co-morbidities that might interfere with study interpretation; to furnish a more homogenous study population that allows a focused characterization of the QDOT MICRO™ catheter for the treatment of PAF; exclude subjects with a medical history or condition that increases their risk of adverse events. Subjects will be evaluated for presence of left atrial thrombus prior to the procedure. Additionally, using esophageal monitoring techniques will be used while ablating the posterior wall, thus minimizing risk of injury.

Participating investigators will be experienced and highly skilled in performing electrophysiology studies, intracardiac mapping and ablation of AF with the use of RF ablation catheters. Each site's Principal Investigator will have satisfied the established training criteria. 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 complication. 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.

6.4.3 Precautions

Invasive electrophysiological evaluation and catheter ablation may impart some degree of risk to the subject. The risk of serious complications is generally related to the severity of cardiac disease. The degree of risk of the electrophysiological and catheter ablation procedures versus the potential benefit of the treatment of a paroxysmal or recurrent arrhythmia should be determined by a qualified physician. Cardiac catheterization and electrophysiological procedures should be performed by qualified and appropriately trained personnel in an electrophysiology laboratory. The laboratory should contain sufficient resuscitative equipment and facilities to manage most potential complications. Failure to observe the contraindications, warnings, and precautions in these instructions and the IFU may result in procedural complications. Immediate risks from ablation treatment may include: cardiovascular injury or perforation with or without cardiac tamponade, pulmonary embolus, tricuspid regurgitation, myocardial infarction, bleeding at the catheter insertion site, sepsis, and death.

Contraindications for catheter ablation of arrhythmia include: existing hemodynamic instability, bacteremia, coagulopathy, prosthetic tricuspid valve, intra-atrial or venous thrombosis, and pregnancy.

6.5 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[4]. 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[53]. However, the guidelines also present that randomized trials showed only modestly improved rhythm outcome with catheter ablation compared to antiarrhythmic drug therapy[53].

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 with the force-sensing technology also incorporates six thermocouple temperature sensors and three micro electrodes embedded in the 3.5 mm tip electrode.

The measured temperature allows the operator to assess the efficiency of ablation in real time. Thus providing a highly sensitive measure of catheter location stability and/or movement during RF application and potentially reducing the need for additional RF applications.

The micro electrodes provide high quality localized electrograms that allow finer endocardial electrical mapping and 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.

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 improved contact force information and temperature feedback in any tip tissue orientation, the new QDOT Micro™ catheter is designed to create durable lesions, in shorter time thus reducing the procedural time, and improved irrigation flow with reduction in the amount of fluid load in the patient as compared to a typical irrigation ablation catheter. The catheter also limits conductive heating and collateral damage to neighboring structures including non-cardiac adjacent tissues, improving safety during the procedure[14, 19, 54]

7.0 STUDY OBJECTIVES AND PURPOSE

7.1 Purpose

The purpose of this study is to demonstrate the safety and 12-Month effectiveness of the QDOT MICRO™ catheter when used with the nMARQ™ RF generator in the treatment of drug refractory symptomatic paroxysmal atrial fibrillation (PAF) during standard electrophysiology mapping and RF ablation procedures.

7.2 Objectives

The primary objective of this clinical investigation is to demonstrate the safety and 12-month effectiveness of the QDOT MICRO™ catheter when used with the nMARQ™ RF generator for pulmonary vein isolation (PVI) in the treatment of subjects with paroxysmal atrial fibrillation (PAF).

- To demonstrate the safety based on the proportion of subjects with early-onset (within 7 days of ablation procedure) primary adverse events
- To demonstrate the 12-month effectiveness based on the proportion of subject with freedom from documented atrial arrhythmia (atrial fibrillation (AF), atrial tachycardia (AT) or atrial flutter (AFL)) episodes during the effectiveness evaluation period (Day 91-365)

The major secondary objectives of this study are:

- To evaluate the incidence of (serious) adverse events during and after procedure up to 3 months following procedure.
- To evaluate Acute Procedural Success as defined by:
  - The % of subjects with electrical isolation of PVs (entrance block) at the end of the procedure, and
    - The % of subjects with electrical isolation of PVs (entrance block) using QMODE+ as the only ablation strategy
    - The % of subjects with electrical isolation of PVs (entrance block) at all power settings combined
  - The % of subjects with electrical isolation of PVs (entrance block) after first pass isolation, after waiting period and adenosine challenge

8.0 STUDY DESIGN AND ENDPOINTS

8.1 Description of the Study Design

The QDOT study is a prospective, multicenter, non-randomized clinical evaluation of the QDOT MICRO™ catheter in treating subjects with symptomatic PAF who have failed at least one antiarrhythmic drug.

Main Study

Up to 185 subjects will be enrolled at up to 30 sites. A Cardiac CT/MRA image subset will be integrated within the Main Study.

Second (Variable flow) Study

Up to 92 subjects will be enrolled at up to 26 sites.

Both Studies

Effectiveness and safety endpoints have been defined and will be compared to predetermined performance goals. Subjects who sign informed consent are considered enrolled in the study. Enrolled subjects who satisfy all eligibility criteria will then undergo the ablation procedure with the QDOT MICRO™ catheter.

After the study ablation procedure, subjects will enter a 3-Month blanking period (Day 0-90).

After the Blanking Period, subjects will enter the Evaluation Period (Days 91-365). Subjects having AF recurrence and/or receiving therapeutic interventions during the evaluation period will be considered effectiveness failures (refer to Section 8.2.2 for all effectiveness failure modes).

All subjects will undergo follow up visits at defined intervals (refer to Table 13.8A Schedule of Treatments and Evaluations). Subjects complete the IDE study after the 12-month follow up visit.

8.1.1 Cardiac CT/MRA Subset

Main Study

At a subset of sites, subjects from the Main Study will be enrolled in the cardiac CT/MRA subset and will undergo a 3-month CT/MRA in addition to the baseline CT/MRA (all subjects will have a baseline CT/MRA) to assess incidence of post-ablation severe PV stenosis. In order to be included in the cardiac CT/MRA population, the subject must have readable outcomes at baseline and 3 months. The first 40 subjects consecutively enrolled in the Main Study (included in the 185 total) at cardiac CT/MRA subset sites who have readable outcomes will be included in the CT/MRA subset (until sufficient CT/MRA subjects are accrued). The probability of observing at least one moderate/severe PV stenosis with 40 subjects is 87% assuming the event rate of moderate/severe PV stenosis is 5%.

In addition to this subset, any subjects with signs or symptoms of PV stenosis will undergo a post ablation CT/MRA. These subjects will not be included in the CT/MRA subset analysis. If severe PV stenosis is present it will be reported as an adverse event.

8.2 Study Endpoints

8.2.1 Primary Safety Endpoint

The primary safety endpoint is the incidence of any primary adverse event occurring within 7 days of the AF ablation procedure (including the initial and repeat procedures), using the QDOT MICRO™ catheter per protocol, except atrio-esophageal fistula and PV stenosis, which may also be considered as primary adverse events if occurring greater than seven (7) days and up to 90 days post the ablation procedure.[55, 56]

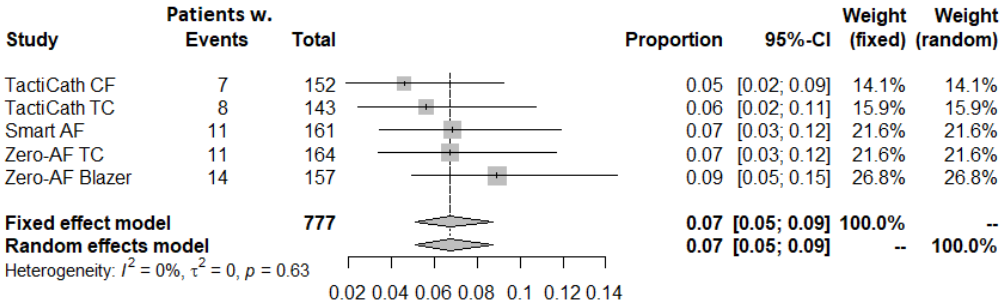
Primary adverse events include the following conditions (refer to Table 14.2.1A: Primary Adverse Events for detailed instructions for defining these adverse events):

- Death
- Atrio-esophageal fistula
- Cardiac Tamponade*+/Perforation+
- Myocardial infarction (MI)
- Stroke / Cerebrovascular accident (CVA) †, ††
- Thromboembolism
- Transient Ischemic Attack
- Phrenic Nerve Injury/Diaphragmatic paralysis
- Heart block
- PV stenosis
- Pulmonary edema (Respiratory Insufficiency)
- Vagal Nerve Injury
- Pericarditis
- Major vascular access complication / bleeding

* Hemodynamic compromise or instability is defined as Systolic BP < 80 mm Hg.
+ Cardiac Tamponade/Perforation occurring within 30 days of the AF ablation process will be considered Primary AEs
† Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.
†† Modified Rankin score assessments should be made by certified individuals.

Data from recent clinical trials for devices similar to the device in the current study were reviewed as a first step to deriving the performance goal for the safety endpoint. A meta-analysis approach was taken to estimate the average composite endpoint rate. Figure 8.2.1 presents the results of the meta-analysis for combining the safety rates. Based on the plot, the upper bound of the 95% confidence interval was estimated to be equal to 9%. The proposed performance goal of 14% would reflect an approximately 50% increase in risk from the upper bound of the 95% CI. Details of the meta-analysis can be found in Appendix C.

Figure 8.2.1 Meta-analysis results



8.2.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is defined as the freedom from documented atrial fibrillation, atrial flutter and atrial tachycardia (AF/AFL/AT) (hereinafter collectively referred to as “atrial tachyarrhythmias") recurrence (episodes ≥ 30 secs on TTM or continuously recorded on the standard 12-leads ECG) during the evaluation period (Day 91-365) and freedom from the following failure modes:

- Acute procedural failure, including:
  - Failure to confirm entrance block in all pulmonary veins post-procedure,
  - Use of a non-study catheter to treat left atrial ablation targets and cavo-tricuspid isthmus
- Repeat ablation failure, including:
  - > 2 repeat ablation procedures with the study catheter during the 3-Month Blanking Period (Day 0-90) after the index ablation procedure.
  - Use of a non-study catheter to treat study arrhythmia ablation targets during the blanking period
  - Any repeat ablation procedure during the Evaluation Period.
- AAD failure: Taking a new AAD for AF or a previously failed AAD at a greater than the highest ineffective historical dose for AF during the evaluation period (refer to section 13.1 for details).

This study is designed to compare the primary effectiveness of the QDOT MICRO™ Catheter to a pre-determined performance goal of 50%, which is indicated as the

minimum acceptable success rate at 12 months for a paroxysmal AF population in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE consensus statement.

8.2.3 Secondary Endpoints(s)

The secondary endpoints will apply to both studies.

8.2.3.1 Secondary Safety Endpoints

- Incidence of Unanticipated Adverse Device Effects (UADEs)
- Incidence of Serious Adverse Events (SAEs) within 7 days (early onset), >7 to 30 days (peri-procedural) and >30 days (late onset) of initial ablation
- Incidence of bleeding complication (ISTH definitions): a) major, b) clinically relevant non-major and c) minor bleeding

Refer to Section 14.3 for the definition of Serious Adverse Event. Refer to Appendix A: Study Definitions for the ISTH bleeding complications definitions.

8.2.3.2 Secondary Effectiveness Endpoints

- Acute Procedural Success

Acute procedural success is defined as confirmation of entrance block in all PVs.

  - % of subjects with electrical isolation of PVs (entrance block) at the end of the procedure
    - The % of subjects with electrical isolation of PVs (entrance block) using QMODE+ as only ablation strategy
  - % of subjects with electrical isolation of PVs (entrance block) after first encirclement (evaluated prior to the 20-minute waiting period and adenosine challenge
  - % of subjects with electrical isolation of all PVs (entrance block) after first encirclement without acute reconnection, after waiting period and adenosine challenge
  - % of subjects and % of PVs with touch-up (i.e. touch-up is used to remove ablation of acute reconnection) among all targeted veins and touch-up location
  - Anatomical location of acute PV reconnection after first encirclement

- Repeat ablation procedures during 12-month period post-procedure
  - Incidence (%) of repeat ablation procedures
  - % PVs re-isolated among all the targeted PVs at repeat procedure
  - % repeat ablation procedures requiring new linear lesions and/or identifying new foci outside of initially isolated area among the repeat ablation procedures

- 12-Month Single Procedure Success

- The 12-month single procedure success is defined as freedom from documented AF/AFL/AT recurrence (episodes ≥ 30 secs) during the Evaluation Period after a single ablation procedure and off AADs. Any repeat ablation procedure or AAD therapy will be deemed effectiveness failure for this analysis.

8.2.3.3 Additional Endpoints

- Procedural Data:
  - Total procedure time, PVI time, RF application time, mapping time and RF application time per lesion
  - Total Fluoroscopy Time and Dose
  - Fluid delivered from the study catheter
  - Location of RF applications, number of RF applications
  - Repeat Ablation Rate
  - RF Ablation parameters per application
  - Device(s) utilized (per ablation)
  - VISITAG™ Settings
  - CF range
  - Power range
  - Tag Index Assessment per anatomical region

    NOTE: Tag Index data (Force, Power, and Time) will be collected in the CARTO® 3 System during the ablation procedures. The data will be processed to generate the Tag Index.
- Quality of Life:
  - Quality of Life (QOL) status will be evaluated by assessing AFEQT
- Cardiac CT/MRA Subset
  - Incidence of severe PV stenosis at 3 months post ablation in the CT/MRA subset assessment evaluation. The CT/MRA subset will be included in the main study only.

8.2.3.4 Health Economic Data

The cost and frequency of health care utilization during hospitalization for the study index ablation procedure, as well as any additional hospitalizations during the study period will be collected. Because this data does not support the safety and efficacy of the QDOT MICRO™ catheter, it will not be provided to the Food and Drug Administration (FDA) as part of the IDE reporting.

The hospitalization health care data to be collected may include but is not limited to: copies of the subject's hospital bills (UB04) and/or itemized hospital bills. Subject's admission

date, discharge date, procedure date, ICD-10 and procedure code, Diagnosis Related Group (DRG) assignment and total cost for the hospitalization will be extracted from the forms.

In addition, the sponsor will also collect health economic data associated with follow up care, including any repeat ablation procedure for treating arrhythmia, any inpatient or outpatient visit (including ER admissions) to address post-procedural complications or any procedure related condition and any inpatient or outpatient visit (including ER admissions) related to arrhythmia and cardiovascular conditions.

9.0 STUDY POPULATION

9.1 Subject Selection

9.1.1 Inclusion Criteria

Candidates for this study must meet ALL of the following criteria:

1. Symptomatic paroxysmal AF with one electrocardiographically documented AF episode within 6 months prior to enrollment and a physician's note indicating recurrent self-terminating AF within 7 days. Documentation may include electrocardiogram (ECG); Transtelephonic monitoring (TTM), Holter monitor or telemetry strip.
2. Failed at least one (1) antiarrhythmic drug (AAD) (class I or III) as evidenced by recurrent symptomatic AF, contraindicated, or intolerable to the AAD.
3. Age 18 years or older.
4. Signed Patient Informed Consent Form (ICF).
5. Able and willing to comply with all pre-, post-, and follow-up testing and requirements.

9.1.2 Exclusion Criteria

Candidates for this study will be EXCLUDED from the study if ANY of the following conditions apply:

1. Previous surgical or catheter ablation for atrial fibrillation.
2. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause.
3. Patient on amiodarone at any time during the past 3 months prior to enrollment.
4. Previously diagnosed with persistent or long-standing persistent AF and/or Continuous AF lasting > 7 days
5. CABG surgery within the past 6 months (180 days).
6. Valvular cardiac surgical/percutaneous procedure (i.e., ventriculotomy, atriotomy, valve repair or replacement and presence of a prosthetic valve).
7. Any carotid stenting or endarterectomy within the last 6 months.
8. Documented LA thrombus on imaging (within 48 hr prior to a study ablation procedure).
9. Documented LA size > 50 mm (parasternal long axis view).
10. Documented LVEF < 40%.

11. Contraindication to anticoagulation (e.g. heparin)
12. History of blood clotting or bleeding abnormalities
13. MI/PCI within the past 2 months (60 days)
14. Documented thromboembolic event (including TIA) within the past 12 months (365 days)
15. Rheumatic Heart Disease
16. Uncontrolled heart failure or NYHA function class III or IV
17. Severe mitral regurgitation (Regurgitant volume ≥ 60 mL/beat, Regurgitant fraction ≥ 50%, and/or Effective regurgitant orifice area ≥ 0.40cm^2)
18. Awaiting cardiac transplantation or other major cardiac surgery within the next 12 months (365 days)
19. Unstable angina
20. Active systemic infection or sepsis
21. Diagnosed atrial myxoma or presence of an interatrial baffle or patch.
22. Presence of implanted ICD/CRT-D.
23. Significant pulmonary disease, (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces chronic symptoms.
24. Severe Gastroesophageal Reflux Disease (GERD; active requiring significant intervention not including OTC medication)
25. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study.
26. 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 study.
27. Enrollment in an investigational study evaluating another device, biologic, or drug.
28. Presence of intramural thrombus, tumor or other abnormality that precludes vascular access, or manipulation of the catheter.
29. Presence of an inferior vena cava filter.
30. Presenting contra-indication for the devices (e.g. TTE, CT, etc.) used in the study, as indicated in the respective instructions for use.
31. Life expectancy less than 12 months

9.2 Strategies for Recruitment and Retention

Main Study

The QDOT MICRO™ IDE study seeks to enroll up to 185 subjects in the study at up to 30 clinical sites in the US. Once enrolled, each subject will participate in the study for 12 Months.

Centers will be selected for participation in the study based on experience with RF focal catheter technology, ablation experience, their capacity to screen and enroll a reasonable number of eligible patients, and ability to perform the required procedures, according to this protocol.

Historically, women and minorities have been underrepresented in or excluded from many clinical studies, leading to a lack of information for women and their physicians regarding the risk and benefits of many medical treatments and diagnostic procedures. It is the Sponsor's intent to apply the principles from FDA's guidance titled Evaluation of Sex-Specific Data in Medical Device Clinical Studies in this clinical trial to ensure adequate representation of women and minorities. The Sponsor will take reasonable steps to ensure adequate representation of women and racial or ethnic minorities in this clinical trial:

In order to reflect the gender ratio of the intended population, Sponsor plans to enroll approximately 70% males and 30% females in the study. The gender ratio (male: female = 7:3) undergoing ablation procedures in the AF population is estimated based on previous studies.[57]

Sites will be instructed to screen all subjects who may be eligible for participation in the study without regard to sex or race. Statistical analysis of primary safety and effectiveness endpoints will be carried out to evaluate any interaction between treatment and gender. Subjects will be encouraged to remain in the study until they have completed the protocol required follow-up period.

Sponsor will attempt to include a diversified group of research sites engaging a variety of academic and private institutions geographically located throughout the US and possibly other regions. To ensure generalizability of results and minimize the influence of any single site, no more than approximately 15% of the total enrollment will be allowed at a single site.

Second (Variable Flow) Study

Centers that have enrolled subjects in the main arm of the study will be allowed to enroll subjects into the second (variable flow) study. The 15% site enrollment cap also applies to the second (variable flow) study.

9.3 Subject Withdrawal/Early Termination

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.

9.4 Subjects Lost to Follow up

Subjects should be encouraged to return for protocol required, clinic visits for evaluation during the study follow-up period. If a subject is unable to return for an office or clinic visit or unable to 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 requesting the subject's continuation in the study or confirming the subjection desire to terminate from the study.

If the subject does not respond to the phone telephone calls or letter, then the subject will be considered "lost to follow-up."

9.5 Subject Disposition

A subject is considered enrolled when they sign the informed consent. Because the treatment assignment is the same for both studies the subject disposition does not change for the second (variable flow) study.

- **Enrolled Subjects**: subjects who sign the informed consent.
- **Excluded Subjects**: subjects that are enrolled but never undergo insertion of the study catheter. Excluded subjects will not be included in the safety evaluation of the study catheter.
- **Discontinued Subjects**: subjects that have the study catheter inserted but are not treated with the study catheter (i.e., no RF energy applied). These discontinued subjects will be followed for 3 months and be part of the safety evaluation.
- **Evaluable Subjects**: enrolled subjects who meet the eligibility criteria and undergo ablation with the study catheter.
- **Lost to Follow-up Subjects**: subjects who are enrolled, but contact is lost after most recent follow-up visits (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 or are terminated from the study prior to completion of all follow-up visits.
- **Completed Subjects**: enrolled subjects who completed the 12-month follow-up visit and have not been excluded, discontinued, withdrawn, early terminated, expired or lost-to-follow-up from the study prior to the final study visit.

10.0 RESPONSIBILITIES

10.1 Study Timelines

Study Duration: The study is expected to last approximately 20 months (8-9 months for enrollment for main study and 5 months for the second study; 12 months of follow-up for primary endpoint for each study).

10.2 Investigator Responsibilities

The Principal Investigator is responsible for supervision of all study activities and is ultimately responsible for overall compliance with protocol, GCP, local and regional regulations, and IRB/REB requirements. Many study activities may be formally delegated to support staff, but the Principal Investigator retains responsibility for supervision of all study activities.

Specific responsibilities include:

- Obtaining IRB/REB approval and renewals
- Providing Sponsor with:
  - Written IRB/REB approval letters and IRB/REB-approved consent forms,
  - Signed, dated Investigator Agreement,
  - Signed and dated Financial Disclosure form at study outset and any time financial changes occur, for up to one year following completion of the study
  - Curriculum vitae for each Investigator and key research staff member
- Maintaining an accurate and current Study Personnel Log which identifies all individuals authorized to perform work for the study at each site
- Completing appropriate training on the study device and the study protocol prior to enrolling and treating subjects
- Maintaining accurate and current logs for the study as requested by the study team, including but not limited to:
  - Subject screening log
  - Device Accountability log
- Obtaining informed consent (including privacy language) from patients
- Performing the ablation procedure
- Complying with the clinical protocol
- Notifying the Sponsor and IRB/REB of adverse events, deaths, and deviations as defined in this protocol and per IRB/REB requirements.
- Notifying Sponsor promptly of withdrawal of IRB/REB approval
- Complying with IRB/REB (as applicable) and Sponsor annual report requirements

- Completing eCRFs accurately and as soon as possible after collection of data
- Reviewing and signing designated eCRFs
- Maintaining relevant source documentation to support future verification of data on the eCRFs.
- Complete all subject follow-up visits, including efforts to maintain contact with subjects who fail to comply with the follow-up schedule. Before a subject may be classified as 'lost to follow-up', the Investigator or authorized personnel should document attempts to contact the subject.
- Retaining study records as described in section 22.1. The Sponsor will notify the Investigator when records may be destroyed.
- Preparing a final report and periodic IRB/REB updates as required

10.3 Sponsor Responsibilities

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

- Preparing of study documents including but not limited to the protocol, eCRFs and template informed consent, if no local template is preferred
- Completing pre-study site assessments and approvals
- Obtaining approval from the FDA and regional Health Authorities (HAs)/ Regulatory Authorities (RAs)
- Providing protocol training to investigators and research personnel
- Instructing operators and technicians in the proper use and monitoring of study devices
- Monitoring the study throughout the duration of the investigation
- Securing investigator/site compliance with the protocol and applicable regulations
- Creation and maintenance of eCRF database
- Conducting all communications with HAs/RAs
- Submitting study supplements for regulatory approval (as necessary), e.g., request for study expansion
- Preparing reports summarizing the status of the clinical study no less often than annually, which will be supplied to the FDA and to other HAs/RAs as requested. Annual reports may also be provided to each HA/RA, and possibly to the Principal Investigator as requested
- Report the results of an evaluation of an unanticipated adverse device effect to FDA within 10 working days after receiving notice of the adverse effect.
- Access to clinical study data provides opportunities to conduct further research that may help advance medical science and improve patient care. This helps

ensure the data provided by research participants are used in the creation of knowledge and understanding. To this end, the study results on all pre-specified outcomes, including negative outcomes, will be submitted to ClinicalTrials.gov no later than one year after completion of the primary endpoint (unless an extension has been approved via certification from the Secretary of Health and Human Services). Results submission could be delayed if an extension is granted to the results submission deadline; however, the release of all results on pre-specified outcomes will be hastened if the study is terminated early

10.4 Training

10.4.1 Research Team

The training of appropriate clinical site personnel will be the responsibility of the Sponsor or the Sponsor's representative. In some cases, training may be performed by an existing site staff member who has already been trained by the Sponsor (such as assigning a new CRC to the study). To insure uniform data collection and protocol compliance, the Sponsor will present a formal educational session to study site personnel that will include review of the Clinical Study Protocol, techniques for the identification of eligible subjects, instructions on in-hospital data collection, follow-up schedules, and regulatory requirements. Remote as well as on-site contacts will be used to monitor study performance indicators such as enrollment compliance, data submission rate, data errors, protocol questions, and GCP compliance.

10.4.2 Investigator Training

QDOT MICRO™ Catheter Training:

The training of applicable clinical site personnel will be the responsibility of the Sponsor. Prior to initiating subject enrollment at a site, appropriate study training will be provided. Investigators selected to participate in the study will be experienced in intracardiac mapping and AF ablation with focal ablation catheters. Investigators will undergo device training in accordance with the physician training charter.

To ensure uniform data collection and protocol compliance, the Sponsor will conduct a training session that will include reviewing the protocol, eCRF and data collection process, and the adverse event reporting process. The sponsor will reinforce the training or provide clarification throughout the study, as needed.

11.0 STUDY DEVICE DESCRIPTION

11.1 Device Acquisition

After obtaining a fully executed clinical trial agreement and appropriate approvals, the Sponsor may initiate shipment(s) of investigational devices 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 investigator or

designee. Site study personnel are responsible for appropriate logging of the devices received, verification of packing slip information (i.e., lot numbers and quantity shipped), recording the date of use and subject ID for each device used in the study, and recording device disposition information regarding disposal or return to the Sponsor.

11.2 Device Storage and Stability

Investigational Devices are to be stored in a secure/locked location. All devices are to be stored in accordance with the IFU. Do not use any devices after the "Use By" date.

11.3 Instructions for Use (IFU)

A copy of the IFU for the QDOT MICRO™ catheters and interface cable is included in each product package.

11.4 Device Description

11.4.1 QDOT MICRO™ Catheter

The Biosense Webster QDOT MICRO™ Catheters are 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. The catheter shaft measures 7.5 F with 8 F ring electrodes. For ablation, the catheter is used in conjunction with a compatible RF generator and a dispersive pad (indifferent electrode). The catheter has force-sensing technology that provides a real-time measurement of contact force between the catheter tip and the heart wall.

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 11.4.1A Overview of the QDOT MICRO™ Catheter with both Uni-directional and Bi-directional Tip Deflection

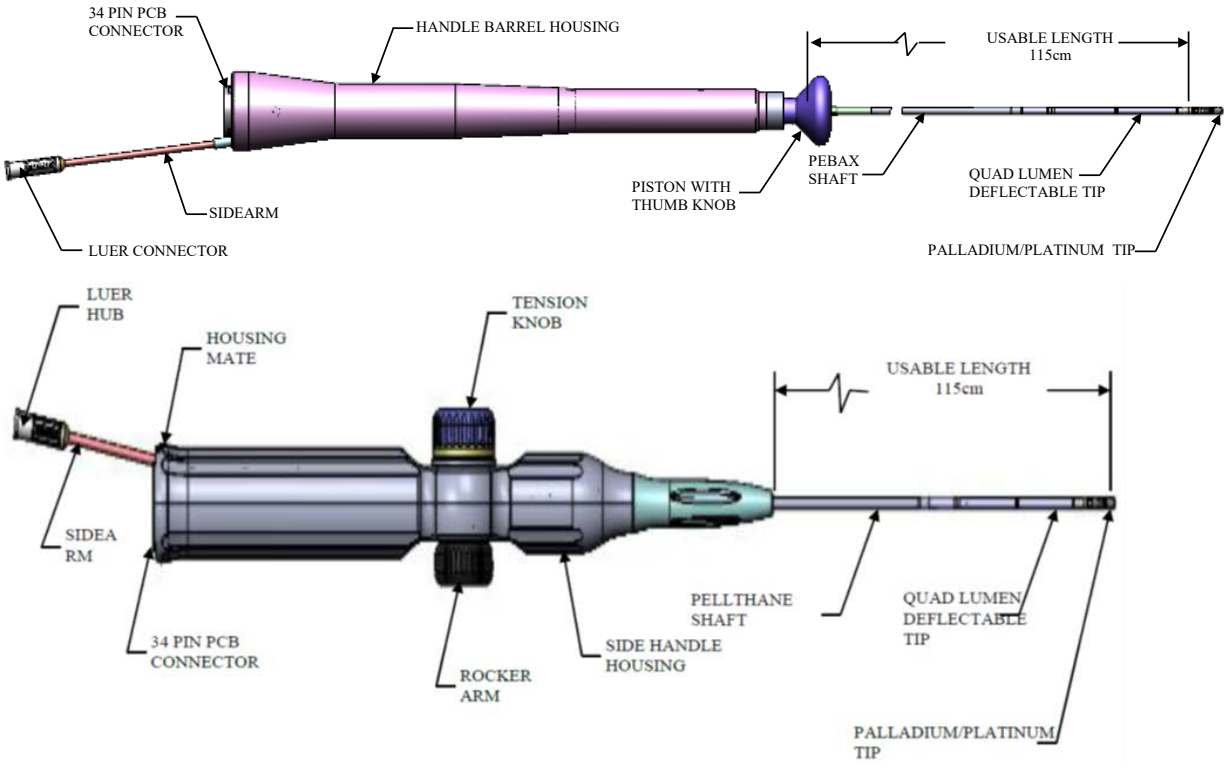
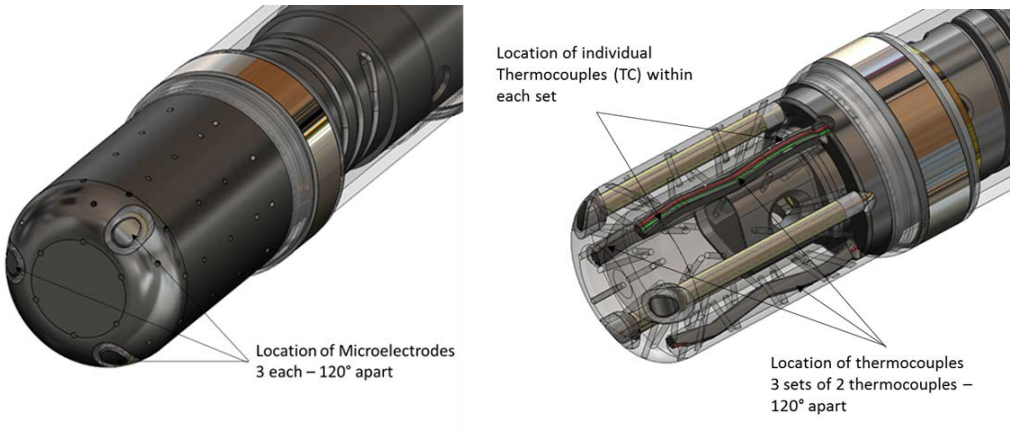


Figure 11.4.1B QDOT MICRO™ tip Section

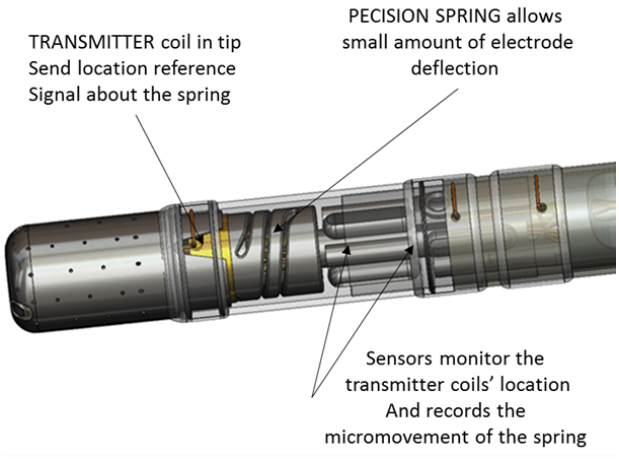
Figure 11.4.1C QDOT MICRO™ tip with Thermocouples (6), µElectrodes (3) and angled irrigation ports



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 v6 Navigation System (refer to Figure 11.4.1D). 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 v6 Navigation System.

Figure 11.4.1D 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 (COOLFLOW® Irrigation Pump) RF Generator (nMARQ RF Generator), and required cables, refer to the respective Instructions for Use and/or User Manual.

Refer to Section 11.5 (Required Study Equipment) for details on additional equipment required for this study.

11.4.1.1 Bi-directional Catheter Description (D-1395-XX-SI)

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.

11.4.1.2 Uni-directional Catheter Description (D-1394-XX-SI)

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.

11.4.2 nMARQ® Multi-channel RF Generator (D-1341-07-I)

The nMARQ® Multi-channel RF generator software version 3.0.1 (main study) and version 3.0.6 (second [variable flow] study) are intended for cardiac ablation applications. Its purpose is to generate RF energy for delivery to a site in the heart via compatible RF ablation catheters. The generator includes functions for controlling ablation parameters at

the ablation electrodes of the catheter. Ablation parameters, such as power, impedance, ablation duration, and temperature are recorded and can be exported at the end of the procedure to a USB device.

The generator consists of the following main components:

- **Console**: The console contains the hardware that provides the delivery of RF energy.
- **Local Control Workstation (Local Monitor)**: The local monitor contains a touch screen user interface. The monitor contains the software that controls the generator and tells the console what function to perform. It also provides communication with the CARTO® 3 workstation and the Remote Control Workstation. The local monitor attaches directly to the console.
- **Remote Control Workstation (Remote Monitor, optional)**: The remote monitor is physically the same as the local monitor. The remote monitor connects to the local monitor via a connecting cable which allows the remote monitor to be used outside of the patient area. The only differences between the local and remote monitors are:
  - Log files can only be copied from the local monitor, not the remote monitor.
  - Technician settings are accessible only from the local monitor.
  - Only the local monitor communicates to the console. The remote monitor passes the user inputs to the local monitor that then passes the inputs to the console. Further, when the "Stop" button is pressed on the remote monitor, the signal is passed directly from the remote monitor to the console through the local monitor but without any intervention.
- **Foot Pedal**: The foot pedal allows the user to start and stop ablation without pressing the Start and Stop buttons on the monitor.
- **Cart**: The generator's console and local monitor rest on the cart to facilitate movement of the equipment throughout the lab.
- **Connection Cables**: Cables are used to provide an interface between the various components of the generator and to provide connection to an external energy source to allow operation of the generator.

11.4.3 TX eco EXT Interface Cable (D-1357-03-SI)

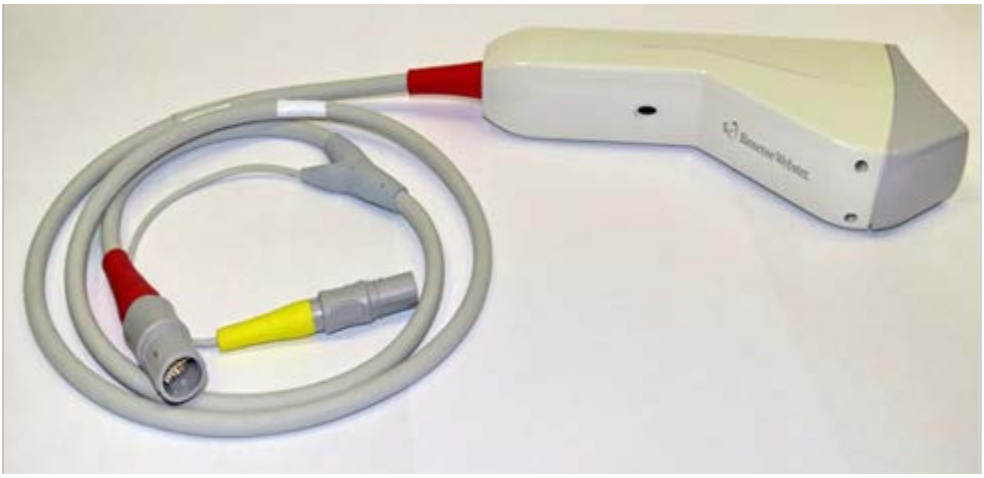
The TX eco EXT Connection Cable (D-1357-03-SI) is designed to connect the QDOT MICRO™ Catheter that interfaces the Patient Interface Unit (PIU) of the CARTO® 3 EP Navigation System via the dongle. The TX eco EXT Connection Cable consists of a gray connector which connects to the dongle and a black connector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

Figure 11.4.3A: TX eco EXT Connection Cable

11.4.4 TX eco Cable Dongle (EM-5050-055F)

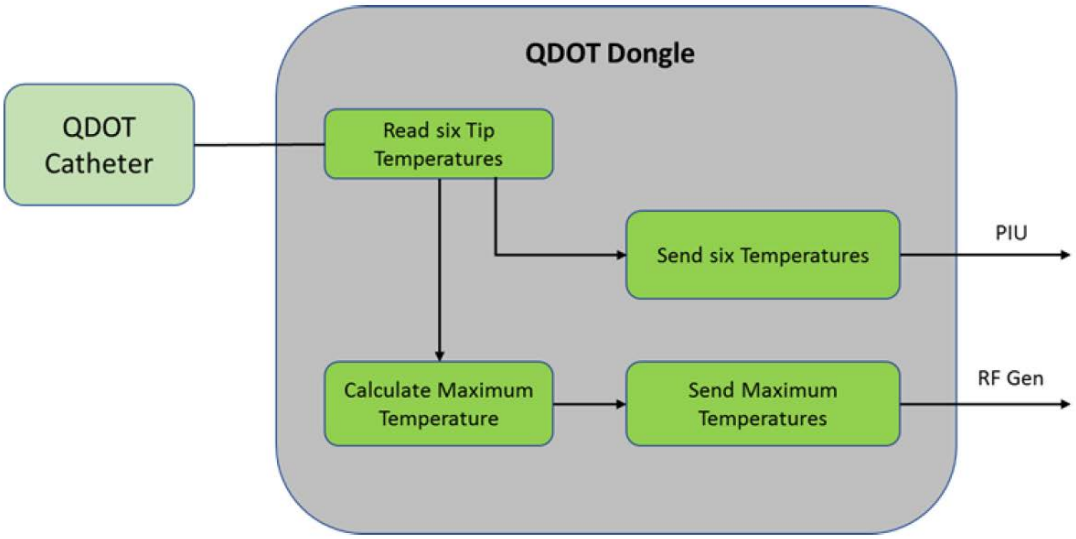
The Biosense Webster TX eco Cable (Dongle) (EM-5050-055F) is an accessory device primarily intended to provide a means for the QDOT MICRO™ Catheter to interface with the CARTO®3 v6.0 EP Navigation System and to the nMARQ® RF generator. The TX eco Cable (Dongle) processes and transfers catheter location 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 11.4.4A: TX eco Cable (Dongle) with Extension Cable



Refer to Figure 11.4.4B below which depicts a functional block diagram of the TX eco Cable (Dongle) signal processing and transfer activities.

Figure 11.4.4B Block Diagram of the TX eco Cable (Dongle) Processing and Transfer Activities



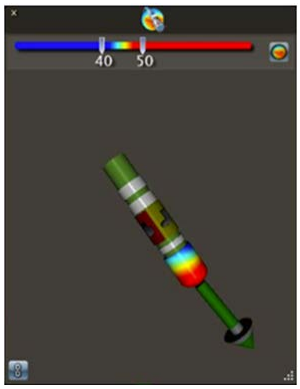
11.4.5 CARTO® 3 v6.0.60 QDOT MICRO™ Software Module

The QDOT MICRO™ software module is an add-on 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.

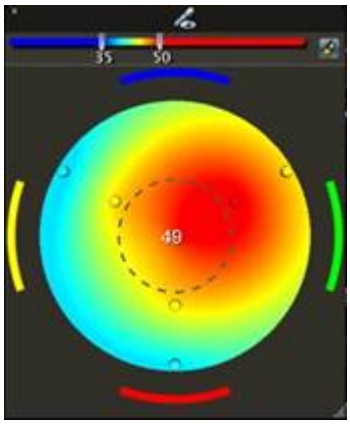
Tip Temperature Display

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 "bulls eye" display.

Figure 11.4.5A: Information Displayed on the Carto 3 System



Colored catheter temperature distribution 3D display



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

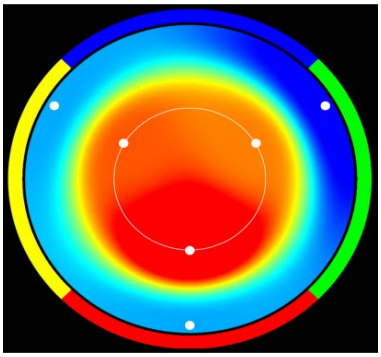
The "bulls eye" display provides temperature information to the physician. An optional numerical value of the temperature from the RF Generator is displayed on the "bulls eye" determined by the physician's preference to display or not to display). The colored graphic of the bull's eye provides relative 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

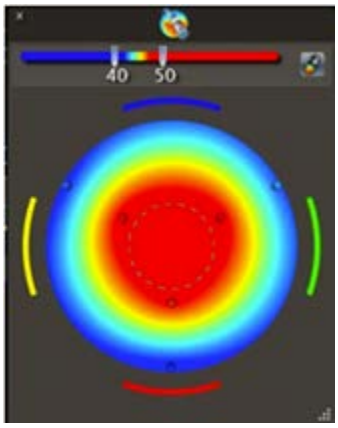
thermocouples: 3 distal and 3 proximal. The inner circle represents the tip electrode and the outer ring represents the tip sides.

Figure 11.4.5B: 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 11.4.5C: 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 in Figure 11.4.5D.

Figure 11.4.5D: Temperature display for Parallel Catheter Tip Orientation

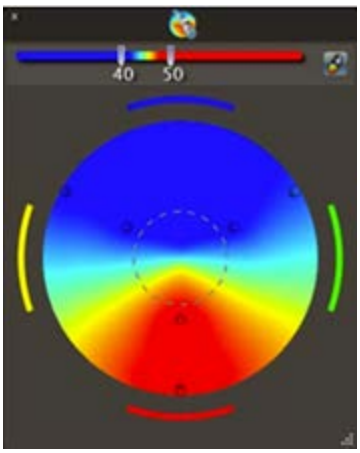
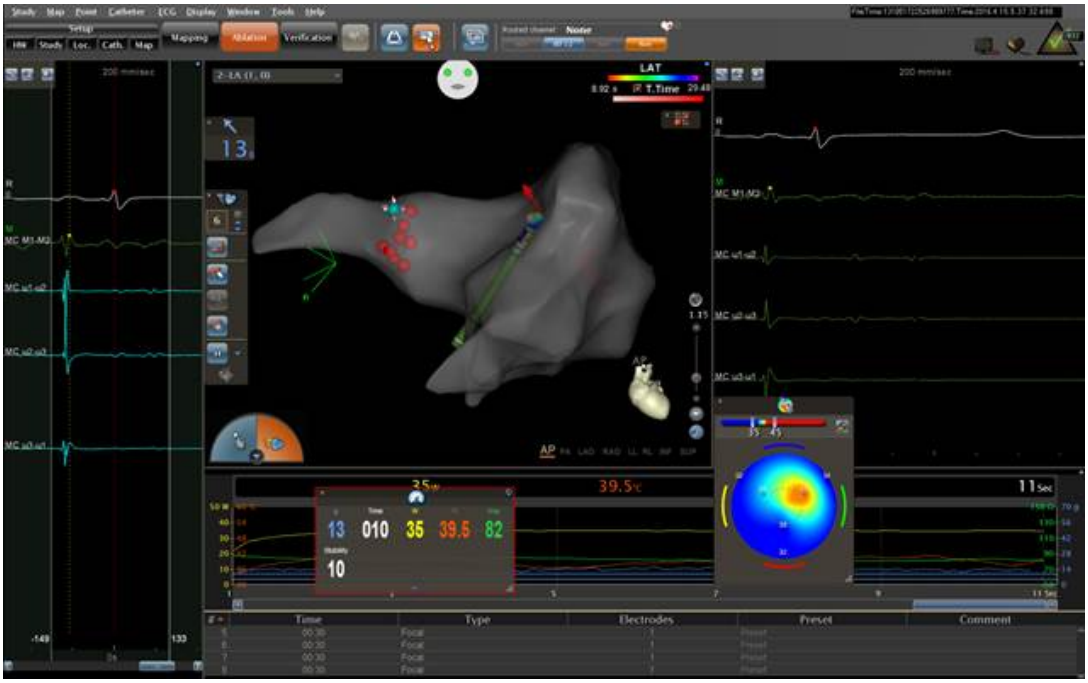


Figure 11.4.5E: CARTO® 3 GUI with RF generator in Unipolar Mode, QDOT MIDRO™ Catheter



11.5 Required Study Devices and Equipment

The following devices are required for the AF ablation procedure during this study:

Table 11.5A: Required Study Equipment

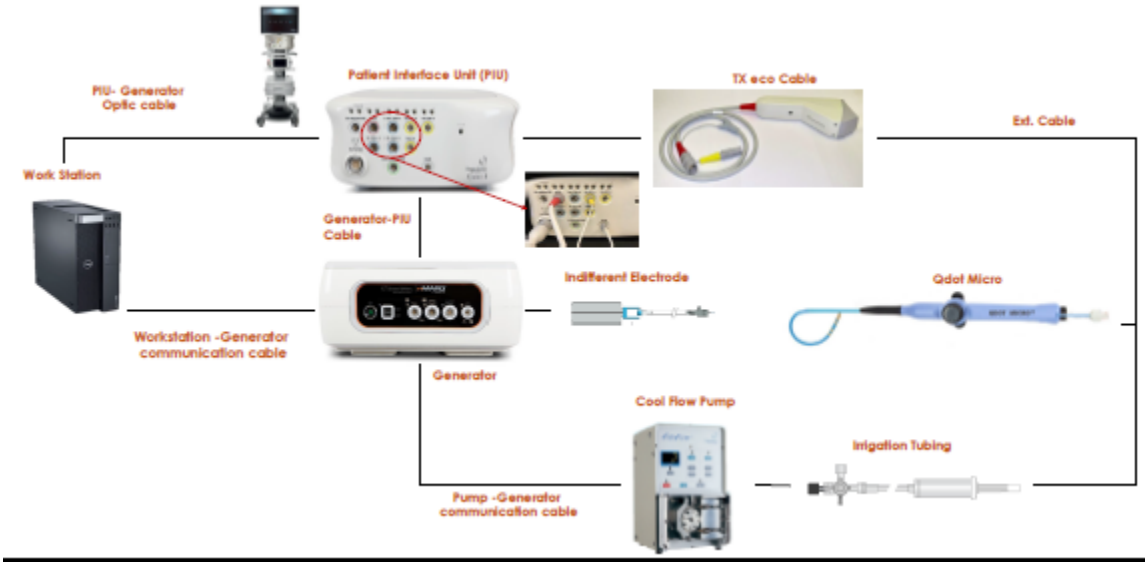
Equipment	Function or Specifics

Investigational Equipment	
QDOT MICRO™ Catheters • D-1394-XX-SI • D-1395-XX-SI	Delivers RF energy to the target tissue.
TX eco EXT Connection Cable (D-1357-03-SI)	Provides a means to interface the QDOT MICRO™ catheters with the Dongle
TX eco Cable (Dongle) (EM-5050-055F)	Provides a means to interface the QDOT MICRO™ catheters to the Multi-Channel RF Generator
nMARQ Multi-Channel RF Generator (D-1341-07-I) • v3.0.1 – Main Study • v3.0.6 – Second (variable Flow) Study	Transmits RF energy to the Ablation Catheter
CARTO 3 v6.0.60 QDOT MICRO™ Software Module	Provides a visual interface for the features of the QDOT MICRO™ 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® system.
CoolFlow® Irrigation Pump and 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 recommended)
Interface Cables	Connection of choice
CARTO® System Junction Box	Provide the interface to the catheter, generator, and the CARTO® System.
Carto® 3 v 6.0 System	For mapping and visualization information. Version 6.0.60 or higher

11.6 System Components and Set-Up

A connectivity diagram for system set up is depicted in Figure 11.6A.

Figure 11.6A: System Set Up



12.0 STUDY MEDICATIONS

12.1 Antiarrhythmic Drugs

12.1.1 Definitions

- Antiarrhythmic drugs (AADs)

The study protocol will classify and analyze the following:

  - Class I drugs (e.g., flecainide, propafenone, disopyramide, etc.)
  - Class III drugs (e.g., amiodarone, dronedarone, dofetilide, etc.)

- Previously Failed AAD

Any AAD that a subject has ever taken for the treatment of his/her AF, prior to enrollment, is considered a "previously failed AAD" if it meets both of the following conditions:

  - prior to enrollment, the AAD was ineffective in controlling the subject's AF or produced intolerable side effects leading to its discontinuation;
  - the AAD is administered for AF

- New AAD

ANY AAD that was never taken for the treatment of AF prior to enrollment is considered a "new AAD" if the drug is administered to treat an "atrial tachyarrhythmia" post-enrollment.

Table 12.1A illustrates the corresponding status of primary effectiveness endpoints based on AAD therapy administered in the blanking and post-blanking periods.

Table 12.1A: AAD Usage and Impact on Primary Effectiveness Classification

	Blanking period **(≤ 90 days post procedure)**	**Post blanking period** **(> 90 days post procedure)**
Class I and/or Class III AAD	**Can** be initiated, continued from prior to study enrollment, or increased in dose as long as the AAD is **stopped on or before day 90 post procedure** and subject will not be classified as a primary effectiveness failure**.**	If initiated for the treatment of **AF**; subject will be classified as a primary effectiveness **failure**. If initiated for the treatment of **AF** during the blanking period and continued past Day 90; Subject will be classified as a primary effectiveness **failure** **Can** be initiated, continued from blanking period, or increased if drug is NOT for the treatment of atrial arrhythmia (e.g. hypertension) other than CTI dependent AFL and subject will not be classified as a primary effectiveness failure.
Class II and/or Class IV AAD	**Can** be initiated, continued from prior to study enrollment, or increased in dose and subject will not be classified as a primary effectiveness failure.	**Can** be initiated, continued from prior to study enrollment, or increased in dose and subject will not be classified as a primary effectiveness failure.

12.2 Study specific anticoagulation requirements

- PRIOR to the procedure
  - Uninterrupted anticoagulation therapy should be in place at least 1 month prior to 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. Any INR < 2 within 3 weeks prior to ablation will lead to exclusion of the subject or postponement of the study procedure until the INR is ≥ 2 for at least 3 weeks prior to treatment.
  - Anticoagulation therapy should not be interrupted or stopped prior to the procedure (this means no doses should be missed or omitted) and daily regimen should be continued.
- DURING the procedure
  - Administer a heparin bolus PRIOR to transseptal puncture.

- Target an ACT of ≥350 seconds prior to inserting the catheter and throughout the procedure.
- ACT levels MUST be checked every 15 - 30 minutes during the procedure to ensure an ACT target of ≥350 seconds. All recordings (ACT level, timing of heparin administration and dose) must be documented in the medical records as source documentation.
- Flush all tubing and sheath continuously with heparinized saline.

- FOLLOWING the procedure
  - Anticoagulation therapy is strongly recommended for at least 2 months following ablation.

13.0 STUDY SCHEDULE, PROCEDURES, AND ASSESSMENTS

13.1 Screening and Informed Consent

13.1.1 Patient Screening

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

Subjects are enrolled upon signing the informed consent form. No subject may undergo any protocol required tests or examinations falling outside the standard of care without first signing the Informed Consent form for this clinical investigation.

Screening for the second (variable flow) study can only begin after enrollment in the main study is complete.

13.1.2 Informed Consent

Signing of an approved Informed Consent form (ICF) or Patient Information/Informed Consent form (PI/ICF) by the study candidate documents the patient's acceptance and enrollment in the study. Prior to signing, the investigator or authorized member of the research team should discuss the background, potential risks and benefits, and expectations of the study with the candidate. The candidate should have any questions answered to his or her satisfaction and should have access to an investigator for technical or medical questions as requested. Sufficient time must be given for this process. The subject or legal representative must sign the consent form prior to conducting any study-specific exams or tests that fall outside of the standard of care. The consent form used must have prior approval from a duly-constituted Institutional Review Board, Regional Ethics Board, or Ethics Committee. Failure to obtain informed consent renders the subject ineligible for participation in the study.

The informed consent will include an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) or as required per local regulations. Subject confidentiality

will be maintained throughout the clinical trial in a way that assures that individual subject data can be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows identification of all data reported for each subject. Data relating to the trial may be made available to third parties, provided the data are treated as confidential and that the subject's privacy is guaranteed.

The informed consent will also request authorization for release of billing information specific to the subject's participation in the study. Specifically, the subject's UB04 (an itemized bill for the study procedure), the explanation of benefits (EOB) and any other hospitalizations or ER visits that occur during the study will be requested for each procedure and/or hospitalization.

13.2 Pre-Procedure/Baseline Assessments, Evaluations and Procedures

Pre-procedure assessments must be performed within 30 days prior to the index AF ablation procedure unless otherwise noted. Some assessments (listed below) have a shorter window prior to the AF ablation procedure.

- **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.).
- **NYHA Functional Class Scale** (for subjects with congestive heart failure).
- **CHA2DS2 VASc Score**: Will be used to assess the risk of stroke
- **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 enrollment but prior to the ablation procedure and should be recorded in the eCRF.
- **Anticoagulation Therapy**: Uninterrupted anticoagulation management is mandatory for each study subject. For subjects on warfarin/coumadin therapy, subjects shall be maintained on Warfarin/Coumadin for at least 3 weeks prior to treatment with an INR ≥ 2 (to be confirmed maximum 48 hours pre-procedure). Any INR < 2 within 3 weeks prior to ablation will lead to exclusion of the subject or postponement of the study procedure. The results must be available prior to start of procedure.
- **Physical Exam** including standardized neurological exam done by a physician (including cranial nerve, motor and sensory function, and gait assessments), must be conducted at the pre-procedure visit
- **NIH Stroke Scale** (NIHSS) administered by certified healthcare provider done pre-procedure

- **Vital Signs**: height, weight, heart rate, body temperature, blood pressure, pulse rate
- **Electrocardiogram**: (12-Lead ECG) Data from 12-lead ECG recordings will be collected if available.
- **Transthoracic Echocardiogram (TTE)**: Imaging to determine the atrial size prior to the AF procedure. If the subject has undergone an imaging procedure within the last 6-months where the atrial size (parasternal long axis view) was assessed and documented, the pre-procedure imaging assessment is not required.
- **Cardiac Multi Slice Computed Tomography (CT) or Magnetic Resonance Angiogram (MRA) image**: CT/MRA will be used to evaluate the number, size and anatomy of the pulmonary veins and the left atrial anatomy in the CT/MRA subset. It is mandatory to conduct the CT/MRA assessment prior to the study ablation procedure. For each PV, a core lab will determine the following measurements:
  - Major axis (mm)
  - Minor axis (mm)
  - Average diameter (mm)
- **Imaging for detection of LA thrombus**: performed within 48 h 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 24 hours prior to the procedure.
- **Baseline Quality of Life (QOL) Assessment**: AFEQT must be collected prior to procedure
- **Adverse Events** must be collected from the time the subject signs the informed consent onwards

13.3 Study Ablation Procedure

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 Study ablation procedure will utilize both QMODE and QMODE+ temperature control modes to treat subjects with PAF. QMODE+ temperature control will be used primarily for PVI. QMODE temperature control will be used primarily for AF application outside the PV ostia and for touch-up of the PVI, if necessary.

Table 13.3A: QMODE and QMODE+ RF and Flow Rate 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**
Second study (Variable Flow Rate)					
90W†	40-60ºC	60ºC	60-70ºC	70ºC	4-15 mL

* 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 to 4 sec. It is recommended to use lower target temp setting for the posterior wall RF applications.

.

Recommendation for CoolFlow® Irrigation Pump Setting and RF Power-delivery

The CoolFlow® Irrigation Pump will deliver a continuous infusion of 2 ml/min of room temperature heparinized saline (1 u heparin/1 ml saline) when not delivering RF energy. Increase the irrigation to high flow rate starting minimal 2 seconds before the onset of RF energy delivery.

Main Study

- QMODE+

For QMODE+ (90W), a flow rate of 8 ml/min will be used. Do not use this catheter without irrigation flow and maintaining this higher flow rate.

- QMODE

For QMODE, a high flow rate starting up to minimal 2 seconds before the onset of RF energy delivery and maintaining this higher flow rate up to 4 seconds after termination of the energy application (refer to Table 13.3A and Section 13.3.5).

Second (Variable Flow) Study

For the second study the flow rate for QMODE+ will incorporate a variable flow rate during RF applications.

- QMODE+

For QMODE+ (90W), a flow rate will begin at 4 mL/min and change to 15 mL/min as temperature dictates. Do not use this catheter without irrigation flow and maintaining the variable flow rate during RF applications.

- QMODE

Flow rate remain the same as described above and in Section 13.3.5.

Recommended Contact Force (CF) Settings

When using the study catheter in QMODE and QMODE+, the recommended Contact Force working range should be between 5 and 30g.
Caution: For safety precautions, it's recommended to not exceed CF values above 30g.
Note: The QMODE and QMODE+ parameters, presented in Table 13.3A, are user-adjustable, in case the investigator deems appropriate.

13.3.1 QMODE+ Recommended Ablation Parameters

In this study protocol, QMODE+ is to be used as the primary mode for pulmonary vein isolation. If the investigator deems QMODE+ unable to achieve PVI, the study catheter in QMODE should be used to complete the procedure. (refer to Section 13.3.5 and Appendix B for QMODE details)

The **circumferential** anatomical approach will be used to isolate all PVs. To minimize the risk of PV stenosis, it is recommended that RF energy applications are at least 1 to 2 cm outside the PV ostium to isolate the left and right-sided PVs. Confirmation of entrance block in all targeted PVs is **REQUIRED**.

Main Study

Table 13.3.1A: QMODE+ RF and Flow Rate Settings during RF applications

Power	Target Temp*		Cut-off Temp		Nominal Irrigation Flow rate
	Range	Maximum allowed	Range	Maximum allowed	
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.
† The study recommends using this power setting for PVI as a primary ablation Strategy. RF applications at this power setting are limited to 4 sec. It is recommended to use lower target temperature setting for the posterior wall RF applications.

Note: The QMODE+ parameters, presented in Table 13.3.1A, are user-adjustable, in case the investigator deems appropriate.

Caution: The parameters provided in this section are based on data obtained from animal studies. Use clinical judgment when using this catheter paying careful attention to catheter

movement, initial impedance, impedance drop, electrogram reduction, time of RF application, and with consideration of individual patient conditions.

Second (Variable Flow) Study

For the second (variable flow) study the flow rate for QMODE+ will incorporate a variable flow rate during QMODE+ RF applications. At the onset of 90W RF application the flow rate will be at 4mL/min. As the temperature approaches the target temperature the flow rate will change to 15 mL/min to maintain the tip temperature within the target range. If the temperature reaches the set cut-off temperature the system will stop RF delivery.

The introduction of the variable flow is the only change to the system. The catheter should be used in QMODE+ as described in the remainder of this section.

Table 13.3.1A: QMODE+ RF and Flow Rate Settings during RF applications

Power	Target Temp*		Cut-off Temp		Nominal Irrigation Flow rate
	Range	Maximum allowed	Range	Maximum allowed	
90W†	40-60ºC	60ºC	60-70ºC	70ºC	4-15mL**

* 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.

† The study recommends using this power setting for PVI as a primary ablation Strategy. RF applications at this power setting are limited to 4 sec. It is recommended to use lower target temperature setting for the posterior wall RF applications.

Note: The QMODE+ parameters, presented in Table 13.3.1A, are user-adjustable, in case the investigator deems appropriate.

Caution: The parameters provided in this section are based on data obtained from animal studies. Use clinical judgment when using this catheter paying careful attention to catheter movement, initial impedance, impedance drop, electrogram reduction, time of RF application, and with consideration of individual patient conditions.

13.3.2 General AF Procedure Guidelines for QMODE+

The AF ablation procedures for this study should follow the sequence below:

- Diagnostic catheter placement
- Electrophysiology study (discretion of investigator)
- Cardioversion if subject is in AF (discretion of investigator)
- CARTO® Respiratory Gating Mandatory (unless using Jet Ventilation)
- Placement of esophageal temperature monitoring device

- Confirmation of ACT in ≥ 350 sec. PRIOR to insertion of the QDOT MICRO™ Catheter into the left atrium and maintained throughout the procedure
- Transseptal puncture
- A left atrial anatomical map is required prior to an ablation procedure in the LA.
    - An anatomical map is not required of triggers outside of the left atrium e.g. SVC/CS etc.
- Introduction of the QDOT MICRO™ Catheter
    - Use the AUTOTAG feature in Carto 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: 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 QMODE+ unable to achieve PVI, the study catheter in QMODE should be used to complete the procedure (refer to Appendix B for details).
    - 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 catheter movement, EGM reduction and/or impedance changes.
    - For ablation in the region of the right superior PV, precautionary measures such as pacing maneuvers are recommended to evaluate proximity to the phrenic nerve.
- Left Atrial ablation and real time PV isolation
- Post ablation a 20-min waiting period is **REQUIRED** before pacing procedure(s) and/or infusion of cardiac medications to induce AF/reconnection (e.g., Adenosine, Isoproterenol 2-20 mcg/min)

- Confirmation of entrance block in all targeted PVs by Lasso® or PentaRay®
- Conduct fluoroscopic (or equivalent) evaluation of the diaphragm

13.3.3 Esophageal Monitoring

REQUIRED: An appropriate strategy to minimize risk of esophageal injury **MUST** be used to ensure the physician has accurate information about the location of the esophagus relative to intended sites of ablation. The method used to localize the esophagus will be collected in the CRFs.
At least one of the following methods **MUST** be used for esophageal localization:

- Use of an esophageal temperature probe,
- Esophageal visualization with CARTOSOUND® and/or ICE,
- Esophageal visualization using barium swallow.

Safety Alert: when esophageal temperature rise observed, please allow necessary time for tissue to cool down, and do not apply additional lesion immediately at the same or nearby location until the temperature returns to baseline.

In the event of Esophageal temperature rise:

1. When esophageal temperature rise observed, please allow necessary time for tissue to cool down, and do not apply additional lesion immediately at the same or nearby location
2. Move away from that spot and ablate the other areas first then return to that spot if isolation is not attained
3. At the investigator's discretion, QMODE may be used with the operator's usual, chosen, posterior wall power and duration, still watching very carefully for temperature rise and not starting until esophageal temperature returns to baseline.
4. Ablate in an area nearby but slightly away from that area if the above 2 steps don't accomplish the task.

Power reduction data and clinical practice associated with posterior wall RF applications will be collected in the CRFs and CARTO® data files for analysis.

NOTE 1: The recommendations provided are based on data obtained from animal and clinical studies. Use clinical judgment when using this catheter paying careful attention to impedance drop, electrogram reduction, time of RF application, and with consideration of individual subject conditions when selecting settings.
NOTE 2: Reduce Power when high contact forces are observed during creation of RF lesions in the left atrium. For CF $\geq$ 20g power should be $\leq$ 35 watts.

13.3.4 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.

Study procedure requirements are outlined below:

- PVI of all PVs are required (acute success)
- Linear ablation lines are only required to treat documented macro-reentry atrial tachycardias and limited to the following targets only:
  - LA roof line
  - MV isthmus line
  - LA floor line
  - CTI
- A right atrial CTI linear ablation is **REQUIRED** in cases with documented typical atrial flutter either prior to or during the procedure.
- Ablation of spontaneous non-PV triggers
- CFAE ablation (left atrial, right atrial and CS) is not recommended
- Ablation of non-PV triggers induced by adenosine or isoproterenol

Prophylactic ablation of empirical sites is not allowed.

All linear lesions require confirmation of bidirectional conduction block by pacing and/or mapping maneuvers.

13.3.5 QMODE Ablation Parameters and Workflow

QMODE temperature control mode will be used for PVI once the investigator deems QMODE+ unable to complete PVI. Additionally, QMODE temperature control mode will be used for all RF applications outside the PV ostia during the study ablation procedure (refer to Section 13.3.4 and Appendix B for additional details).

Table 13.3.5A: QMODE Ablation parameters

Power	Target Temp*		Cut-off Temp		Nominal Irrigation Flow rate
	Range	Recommended	Range	Recommended	
25-35 W	45-50ºC	50ºC	50-55ºC	55ºC	4mL**
36-50W***	45-50ºC	50ºC	50-55ºC	55ºC	15mL**

* 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 30 sec.

QMODE Contact Force (CF) Settings

When using the study catheter in QMODE the recommended Contact Force working range should be between 5 and 30g.

QMODE Ablation Workflow:

- If the temperature increases rapidly, stop RF application immediately
- RF power range of 15-50 Watts (W) is recommended for atrial ablation
- At anatomical locations, not on the LA posterior wall or CS:
  - Maximum allowed power should not exceed 50 W
  - Duration of ablation should not exceed 60 seconds of continuous ablation at a given location
- Move/drag the catheter to a new location when clinically effective ablation is achieved (EGM reduction and/or impedance drop).
- Duration of ablation as well as 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.

Precautions while ablating on the Posterior wall and Coronary Sinus:

- LA posterior wall and close to the esophagus:
  - Start ablation using standard workflow for posterior wall.
  - Move/drag the catheter to a new location if clinically effective ablation is achieved within 20 seconds (EGM reduction and/or impedance drop).
  - Maximum power used SHOULD NOT exceed 35 W, except when using QMODE+.
  - Duration of ablation as well as the decision to interrupt RF power delivery at any time during ablation SHOULD be guided by:
    - Clinical Investigator judgment and monitoring of ablation effectiveness parameters commonly used such as EGM reduction and/or impedance changes
    - Esophageal temperature changes should be monitored by an endo-luminal esophageal probe or method used to move esophagus as needed (refer to Section 13.3.3)
    - Duration of ablation should not exceed 30 seconds on posterior wall.

13.4 Post Ablation

- Verification of entrance block is required for all PVs.
  - **A 20-minute waiting period is REQUIRED from the last RF application at a PV before verification may be confirmed.** If reconduction is noted, additional RF applications should be applied and a second 20-minute waiting period will be required to recheck for entrance block. If reconduction is still noted, additional RF applications may be applied but a third 20-minute waiting period is not required prior to recheck for entrance block.

- To verify entrance block, analyze electrograms in sinus and/or atrial paced rhythm to confirm that no PV potentials are present.
    - Administration of adenosine or isoproterenol after a 20-minute waiting period is **REQUIRED** to rule out dormant conduction.
- Demonstration of entrance block MUST be confirmed and documented by the LASSO® Circular Mapping Catheter or PENTARAY® NAV Catheter.
- **Linear ablation lines** may only be performed to treat documented macro-reentry atrial tachycardias (LA roof line, MV isthmus line, LA floor line, CTI.
    - Bidirectional block must be confirmed and documented
- The ablation procedure is considered complete when confirmation of block is confirmed and documented.
- In addition to the data collected on the CRFs, a CARTO® backup file identified with the subject's study number must be made for each case and sent to the sponsor as part of the data collection.

13.5 Data collection During the Study Procedure

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

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

- RF application-mode per lesion (QMODE+/QMODE/other)
- Number of RF applications with QDOT MICRO™ catheter (total/ QMODE+/QMODE) and with non-study catheter
- Duration of RF applications with QDOT MICRO™ catheter (total/ QMODE+/QMODE) and with non-study catheter
- 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: location, temperature, impedance, power, contact force, RF duration, ablation index, lesion information on CARTO®
- Ablation number on the generator for first RF application and last RF application per target (left PV targets, right PV targets and for targets outside the PV area)
- Ablation parameters for touch-up applications (location, RF application-mode, amount of touch-up applications, duration and associated generator file number)
- Total procedure time (from first femoral puncture to last catheter removal)
- Atrial mapping time

- Fluoroscopy time and dose
- 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; fluid output and net fluid input
- Strategy used to minimize risk of esophageal injury
- Abnormal esophageal temperature rises

13.5.1 Collection of Ablation Procedure data for post-analysis

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

13.6 Repeat Procedures

Repeat procedures may be performed at the discretion of the investigator. Repeat procedures during follow up may be managed per investigator discretion using an approved ablation catheter. The follow-up schedule will remain based on the initial ablation procedure.

13.7 Post Procedure Follow-up Assessments

The subjects will be required to complete follow up visits through 12 months (365 days) post initial ablation procedure. Follow-up schedules will be based on a 30-day month

Follow-up visits should be scheduled according to the following timeframes: 7 day (7D, day 7-10), 1 month ± 7 days (1M, day 23-37), 3 month ± 14 days (3M, day 76-104), 6 months ± 30 days (6M, day 150-210), and 12 month ± 30 days (12M, day 335-395). Follow-up visit schedule will not reset if subject undergoes a repeat AF ablation procedure.

- Prior to hospital discharge:
    - Physical Exam including standardized neurological assessment (including cranial nerve, motor and sensory function, and gait assessment) conducted by a physician must be performed pre-discharge.
        - If neurological assessment demonstrates new abnormal findings as compared to the one performed at baseline, a formal neurological consult and examination with appropriate imaging (i.e., DW-MRI), needs to be done to confirm any suspected diagnosis of stroke.
    - NIH Stroke Scale (NIHSS) must be administered by certified healthcare provider done prior to discharge
    - Occurrence of arrhythmias, if any
    - Electrocardiogram (12-Lead ECG)

- Transthoracic Echocardiogram (TTE), for evaluation pericardium for possible pericardial effusion and/or pericarditis. In the event significant pericardial effusion is identified, subjects should be followed until the condition resolves.
- Cardiac-related concomitant medications (such as AADs, anticoagulation regimen, etc.) All cardiac-related medications prescribed since the ablation procedure till the end of follow-up will be recorded, including the type and name of the medication, associated indications, starting and ending dates of the prescriptions, etc.
- Adverse events, if any
- Collect Subject Hospitalization Billing information (including UB04 and EOB)

- Data will be collected at the 7 day, 1M, 3M, 6M, and 12M follow-up, and at any unscheduled visits via in-clinic, telehealth or phone visit.
  - **Physical Exam:** Exam should be performed at all clinical visits. This includes vital signs reported by the patient via telehealth or phone visit.
  - **Quality of Life questionnaire: AFEQT™** is to be collected at the 3M, 6M , and 12M visits via in-clinic, telehealth or phone visit.
  - **Electrocardiogram** (12-Lead ECG). Data from 12-lead ECG recordings will be collected at the 3M and 12M follow-up visit (standard of care are acceptable). ECG data will be collected at baseline, pre-discharge, and unscheduled visits if completed as standard of care and at 1M and 6M if a clinical visit occurs and ECG is completed as standard of care.
  - **Transtelephonic Monitoring (TTM):** Subjects will be asked to transmit any symptom-triggered episode that occurs from the time they receive the TTM device through the 12M follow-up visit. See Section 13.10 for the TTM transmission schedule. A core lab will be used to evaluate and assess the TTM tracings.
  - **24 Hour Holter:** Holter monitor will be used at the 12M follow-up visit to monitor the subjects' heart rhythm for 24 hours continuously. A core lab will be utilized to evaluate and assess the 24-hour Holter recordings.
  - **Cardiac Multi Slice CT/MRA Image:** CT/MRA will be completed at the 3M follow-up visit for subjects in the Main study CT/MRA subset. In addition, any subjects who have symptoms suggestive of PV stenosis should undergo CT/MRA imaging.
  - **Adverse Events:** AEs must be collected from the time the subject signs the informed consent onwards.
  - **AFL/AT/AF recurrence**
  - **Repeat Ablation:** Any ablation procedure performed after the index procedure will be recorded at 3M, 6M, and 12M follow-up as well as at any unscheduled visits.

- **Health Economic Data** for hospitalizations, ER visits and outpatient visits, if any
    - At each follow-up visit, health economic data to be collected may include, but is not limited to: hospitalization charge (UB04), repeat ablation procedure and/or procedures resulting from the ablation procedure, outpatient visits, and ER visits
- **End of Study Report** (12-Month)

13.8 Standard Tests and Procedures

The required schedule for subject treatments and evaluations is summarized in Table 13.8A.

Table 13.8A: Schedule of Treatments and Evaluations

	Pre- Proced.				Phone Call	Follow-Up Visits (via in-clinic, telehealth or phone visit)				
	Screening / Baseline		Study Abl[1] Day 0	D/C	7 D D7-10	1 M D23-37	3 M D76-104	6M D150-210	12M D335-395	UNS
Visit no.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Informed consent[1]	X									
Inc & Excl Criteria	X									
Demographics	X									
Vital Signs	X									
Physical Exam		X[17]		X[17]		X	X	X[15]	X	X
NIHSS		X		X						
Med History[2]	X				X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Arrhythmias History	X									
ECG		X		X		X	X	X	X	X
Adverse Events[3,4]		X	X	X	X	X	X	X	X	X
CHA_2DS_2-Vasc Score	X									
NYHA Scale		X								
QOL Assessment[5]		X					X	X	X	
Preg Test[6]		X								
LA thrombus Imaging[7]			X[7]							
TTE[8,9]		X[8]		X[9]						
Concomitant Medications[10]		X	X	X	X	X	X	X	X	X
mRS[16]					X[16]	X[16]	X[16]	X[16]	X[16]	X[16]
PV CT/MRA Subset[11]	X						X[11]			
PV Stenosis CT/MRA[11]					X[11]	X[11]	X[11]	X[11]	X[11]	X[11]
Ablation Assessments			X							
Repeat Ablation[18]						X	X	X	X	X
Device Deficiency			X							
Health Economic Data Collection[12]				X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]
AF/AT/AFL recurrence				X	X	X	X	X	X	X
TTM[13]							X	X	X	X

	Pre- Proced.				Phone Call	Follow-Up Visits (via in-clinic, telehealth or phone visit)				
	Screening / Baseline		Study Abl[1] Day 0	D/C	7 D D7-10	1 M D23-37	3 M D76-104	6M D150-210	12M D335-395	UNS
Visit no.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
24-hour Holter									X	
Subject Completion/ discontinuation form[14]									X[14]	

1 Initial ablation procedure should be done within 30 days of consent.
2 Collected to confirm no changes in medical history since last visit
3 AEs collected once consent has been signed Collected to confirm no changes in medical history since last visit.
4 If AE results in hospitalization, health economic data collection is required.
5 Quality of life tools (AFEQT).
6 Pregnancy test must be done on pre-menopausal women only, within 24 hours of the procedure.
7 Subjects should undergo imaging for the presence of LA Thrombus.
8 Imaging TTE to determine the atrial size (if the subject has undergone an imaging procedure within the last 6-months where the atrial size was assessed, the pre-procedure imaging assessment is not required).
9 Post procedure all Subjects will undergo a TTE procedure to assess the pericardium for pericardial effusion and/or pericarditis.
10 Concomitant medications: only cardiac related (anti-arrhythmia drugs, anticoagulation regimen, etc.).
11 PV imaging (CT/MRA) for subjects who have symptoms suggestive of PV stenosis or are in the Main study CT/MRA PV Analysis Subset.
12 Health Economic Data for hospitalizations (UB04), ER visits and outpatient visits, if any.
13 TTM: all symptomatic cardiac episodes should be recorded and transmitted at the time the event occurs. Asymptomatic transmissions should be recorded and transmitted as described in Section 13.10.
14 12-month visit or last completed visit
15 Required only for clinical visit
16 In the event of a stroke the Modified Rankin Score will assess the degree of disability in the subject who suffered the stroke.
17 A standardized neurological assessment (including cranial nerve, motor and sensory function, and gait assessment) is to be done. If this neurological assessment demonstrates new abnormal findings, the patient should also have a formal neurological consult and examination with appropriate imaging (i.e., DW-MRI), used to confirm any suspected diagnosis of stroke.
18 All subjects who undergo a repeat ablation procedure during blanking period with the QDOT MICRO™ catheter will undergo follow-up for Day 7 and 1 month after the ablation procedure.

13.9 Unscheduled visit

If a subject returns for a potential study related cardiovascular or neurological visit outside of the protocol-defined visit schedule provided in Table 13.8A, the visit will be considered "unscheduled" (UNS). An Investigator may request an unscheduled visit in the presence of a new or worsening cardiovascular condition or neurological deficit. If the unscheduled visit is for a repeat ablation procedure, the protocol follow-up schedule is based on the index ablation procedure. For all unscheduled visits, an unscheduled visit eCRF must be completed and the subject must also return for their next scheduled study visit.

13.10 Heart Rhythm Monitoring

ECG, Transtelephonic monitors (TTM) and Holter Monitors will be used to monitor the subjects' heart rhythm post-treatment.

Transtelephonic Monitors (TTM):

Transtelephonic monitors (TTM) will be provided to each subject no later than at the 3-month follow-up visit for scheduled transmissions of heart rhythm status. Subjects will be instructed to transmit all emergent symptomatic cardiac events and follow a detailed schedule if the subject remains asymptomatic post ablation during the Evaluation Period (Day 91-365).

The TTM transmission schedule:

- Subjects will complete a test transmission upon receipt of the TTM device to demonstrate a working understanding of the device.
- Transmission will be performed once every week during the Evaluation Period, starting no later than the month 3 visit through the end of month 5 of the follow-up period. Starting from month 6, subjects will record and transmit once every month until the end of the 12- month follow-up period.
- All symptomatic cardiac episodes should be recorded and transmitted soon after the event occurs during the Evaluation Period (Day 91-365).

13.11 Repeat AF Ablation Procedures

Repeat AF ablations(s) may be performed at the discretion of the physician. The follow-up schedule (Medication Adjustment and Therapy Consolidation periods and exam intervals) will continue based on the initial AF ablation procedure performed, regardless of repeat ablations.

The following assessments should be performed before each procedure:

- Imaging for detection of LA thrombus – performed within 48 hours prior to the procedure (refer to Section 13.2 for details).
- Pregnancy Test – Pre-menopausal women only, performed within 48 hours prior to the procedure.

Note: All subjects who undergo a repeat ablation procedure during blanking period with the QDOT MICRO™ catheter will undergo follow-up for Day 7 and 1 month after the ablation procedure.

13.12 Core Laboratory

A core laboratory will be used to review the ECGs, TTMs and Holter Monitors for the objective evaluation of recurrence of atrial tachyarrhythmias. Evaluations will be reviewed by a physician. AF episodes will be evaluated per the definition included in this protocol. A core lab will also be used to review the CT/MRA images.

14.0 ASSESSMENT OF SAFETY

14.1 Adverse Event Recording

An Adverse Event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) occurring during a clinical study, whether or not related to the study device or ablation procedure.

For the purposes of this protocol, adverse events will be reported and recorded (via eCRF) if any of the following apply:

- Event is vascular, cardiovascular, or neurologic in nature
- The event is a serious adverse event
- Causality is related to:
  - Investigational device
  - Ablation procedure
  - Unknown in nature

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

- Any medical condition that is present at the of screening. Such conditions should be added to the medical history, if not previously reported. However, if the study subject's condition deteriorates at any time during the study, it should be recorded as an AE.
- A trace / trivial pericardial effusion that is asymptomatic, requires no medical intervention, and does not extend hospitalization will not be considered an adverse event
- Recurrence of pre-existing AF/AT/AFL
- AF/AFL/AT recurrence requiring pharmacological or direct current cardioversion at any time throughout the duration of the study. However, new onset of left atrial flutter occurring post-ablation is an AE.

- Re-ablation for AF or pre-existing AFL/AT itself is not an AE, however any complication associated with the repeat ablation procedures is considered an AE and shall be reported within the applicable timelines.

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.

The investigator is responsible for ensuring that all reportable AEs, observed by the investigator/study staff 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 and whenever the physician becomes aware of an event. Investigators will determine, at each encounter, whether any adverse events (AE) have occurred, and judge their seriousness and relationship to the study device and procedure. Each investigator shall provide source documentation as requested by the Sponsor to facilitate reporting and adjudication of these events.

All adverse events meeting the above definitions, regardless of classification, seriousness, intensity, outcome, or causality, must be recorded in the electronic CRF(s) in a timely manner throughout the study. Onset date of the event, its treatment, current status (resolved, stabilized, or ongoing), and assessment of its seriousness and relationship to the device should be provided when available. All AEs will be monitored until they are resolved or stabilized (no further changes anticipated).

14.2 Classification

Any of the following events, and any death or hospitalization while on study, is to be reported to the sponsor immediately. The Sponsor may request additional information after the initial notification.

14.2.1 Primary Adverse Event

A Primary AE is one of the following events occurring within seven (7) days following an AF ablation procedure with the QDOT MICRO™ catheter when used with the nMARQ™ RF generator, except atrio-esophageal fistula and PV stenosis, which may also be considered as primary adverse events if occurring greater than seven (7) days and up to 90 days post the ablation procedure:[55, 56]

Table 14.2.1A: Primary Adverse Events

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Death	Patient death directly related to the device or procedure and occurs at any time during or after the procedure.

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Atrio-Esophageal Fistula	Is defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophagus erosion combined with evidence of a fistulous connection to the atrium such as air emboli, an embolic event, or direct observation at the time of surgical repair. A CT or MRI scan is the most common method of documentation of an atrio-esophageal fistula.
Cardiac Tamponade*+/Perforation+	The development of a significant pericardial effusion during or within 30 days of undergoing an AF ablation procedure. A significant pericardial effusion is one which results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1 cm or more pericardial effusion as documented by echocardiography. Cardiac tamponade should also be classified as "early" or "late" depending on whether it is diagnosed during or following initial discharge from the hospital.
Myocardial Infarction	The presence of any one of the following criteria: • Detection of ECG changes indicative of new ischemia (new ST-T changes or new LBBB) which persists for more than 1 h • Development of a new pathological Q waves on an ECG, and • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Stroke/ Cerebrovascular Accident	Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke. Duration of a focal or global neurological deficit ≥24 h; or <24 h, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; or the neurological deficit results in death. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)† Confirmation of the diagnosis by at least one of the following: • Neurology or neurosurgical specialist • Neuroimaging procedure (MR or CT scan or cerebral angiography) • Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage) Stroke: (diagnosis as above, preferably with positive neuroimaging study) • Minor—Modified Rankin score <2 at 30 and 90 days†† • Major—Modified Rankin score ≥2 at 30 and 90 days
Thromboembolism	Formation of a clot (thrombus) inside a blood vessel causing obstruction to blood flow. The thrombus can migrate (embolus) and obstruct distal vascular sites. Diagnostic tests to help detect thromboembolisms may include but are not limited to angiography (pulmonary or distal), ventilation-perfusion (V/Q) scans, venography, Doppler ultrasonography, spiral CT, and echocardiography.
Transient Ischemic Attack	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 h), always within 24h. Neuroimaging without tissue injury.
Phrenic Nerve Injury / Diaphragmatic Paralysis	Absent phrenic nerve function as assessed by a sniff test. A phrenic nerve paralysis is considered to be permanent when it is documented to be present 12 months or longer following ablation.

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Heart Block	Impairment of AV conduction requiring intervention (e.g. temporary or permanent pacemaker) due to iatrogenic cause (e.g. inappropriate RF application, traumatic maneuvering of catheter or other intracardiac devices).
Pulmonary Vein Stenosis	A reduction of the diameter of a PV or PV branch. PV stenosis can be categorized as mild <50%, moderate 50-70%, and severe 70% reduction in the diameter of the PV or PV branch. PV stenosis (> 70% PV narrowing) regardless of the presence or absence of symptoms and PV stenosis with ≥ 50% PV narrowing when accompanied with relevant symptoms that cannot be explained by other etiologies will be considered a primary adverse event.
Pulmonary Edema (Respiratory Insufficiency)	Respiratory insufficiency resulting in pulmonary complications necessitating intubation or other significant intervention (including diuretics administered specifically for treating pulmonary edema or ICU hospitalization requiring oxygen administration but not intubation) Exclusion criteria include: • Pneumonia – infiltrate, fever and leukocytosis • Acute Respiratory Distress Syndrome
Vagal Nerve Injury	Injury to the vagal nerve that results in esophageal dysmotility or gastroparesis. Vagal nerve injury is considered to be a major complication if it prolongs hospitalization, requires hospitalization, or results in ongoing symptoms for more than 30 days following an ablation procedure.
Pericarditis	Should be considered a major complication following ablation if it results in effusion which leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 h, requires hospitalization, or persists for more than 30 days following the ablation procedure.
Major Vascular Access Complication / Bleeding	**Major Bleeding:** A major complication of AF ablation if it requires and/or treated with transfusion or results in a 20% or greater fall in HCT. **Major Vascular Access Complication:** Defined as hematoma, an AV fistula, or a pseudoaneurysm which requires intervention such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission.

* Hemodynamic compromise or instability is defined as Systolic BP < 80 mm Hg.

+ Cardiac Tamponade/Perforation occurring within 30 days of the AF ablation process will be considered Primary AEs
† Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.
†† Modified Rankin score assessments should be made by certified individuals.

All reported Primary AEs will be monitored until they are adequately resolved or explained.

14.3 Serious AEs

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

- Lead to a death
- Lead to a serious deterioration in the health of a subject that:
  - Resulted in a life-threatening illness or injury
  - Resulted in a permanent impairment of a body structure or a body function;
  - Required in-patient hospitalization or prolongation of existing hospitalization*
  - Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- Lead to fetal distress, fetal death or a congenital abnormality or birth defect.

"Hospitalization" means the event necessitated an admission to a health care facility e.g., with at least an overnight stay. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.

*Planned hospitalization for a condition present prior to the participant's enrollment in the study will not meet the definition of an SAE, but should nevertheless be included in routine study reporting.

14.4 Non-Serious AEs

A non-serious AE is any event that results in minimal transient impairment of a body function or damage to a body structure and does not require any intervention listed under the criteria for "Serious Adverse Event." Non-serious adverse events require routine reporting via EDC.

14.5 Anticipated AEs

An anticipated AE is one that has been reported in previous studies of RF ablation and can be anticipated in this current study as per the risk analysis. Table 14.5A provides a comprehensive list of anticipated AEs.

Table 14.5A: Anticipated Adverse Events

Anticipated Adverse Events
1. Acute Respiratory Distress Syndrome (ARDS)
2. Air embolism
3. Allergic reaction
4. Anaphylactic shock
5. Anemia
6. Allergic reaction to Anesthesia (e.g., hair loss)
7. Apnea - sedation induced
8. Arrhythmia: bradycardia
9. Arrhythmia: tachycardia
10. Arrhythmia: pro-arrhythmias
11. Arrhythmia: ventricular tachyarrhythmia / pro-arrhythmia
12. Aspiration pneumonia
13. Asthmatic attack
14. Atelectasis
15. Atrial fibrillation
16. Exacerbation of pre-existing arrhythmia
17. Atrio-Esophageal fistula
18. Typical atrial flutter
19. Atypical left atrial flutter
20. Atypical right atrial flutter
21. AV fistula
22. Bleeding complications
23. Bleeding requiring transfusion
24. Cardiac arrest
25. Cardiac perforation
26. Tamponade
27. Cardiac thrombo-embolism
28. Cerebro-vascular accident (CVA) / stroke
29. Chest pain/discomfort
30. Complete heart block, temporary or permanent
31. Conduction block: ongoing / resolved
32. Congestive Heart Failure
33. Coronary artery dissection
34. Coronary artery occlusion
35. Coronary artery spasm
36. Coronary artery Thrombosis
37. Death
38. Deep venous thrombosis
39. Dislodgement of ICD (Implantable Cardioverter Defibrillator)
40. Dislodgement of permanent pacing leads

Anticipated Adverse Events
41. Disseminated Intravascular Coagulation
42. Dyspnoea
43. Endocarditis
44. Epistaxis
45. Expressive aphasia
46. Fainting
47. Fatigue
48. Gastro-intestinal NOS
49. Gastric reflux
50. Nausea
51. Gastrointestinal diverticulosis
52. Heart Failure
53. Hematoma (local) /ecchymosis
54. Hemorrhage
55. Hemothorax
56. High / increased creatine phosphokinase (CPK)
57. Hypotension
58. Hypertension
59. Hypoxia
60. Infection, localized
61. Infection, systemic
62. Laceration
63. Leakage of air or blood into the lungs or other organs due to perforation
64. Liver toxicity
65. Mobile strands in Inferior Vena Cava
66. Myocardial Infarction
67. Neurological disorders (tremor)
68. Neurological disorders (poor coordination)
69. Neurological disorders (headache)
70. Obstruction to the vascular system
71. Perforation of the vascular system
72. Damage to the vascular system
73. Pericardial effusion resulting in tamponade
74. Pericardial effusion without tamponade
75. Minor Pericarditis
76. Major Pericarditis
77. Peripheral embolus
78. Peripheral nerve injury
79. Peripheral thromboembolism
80. Phlebitis

Anticipated Adverse Events
81. Phrenic nerve damage
82. Diaphragmatic paralysis
83. Pleural effusion
84. Acute Respiratory Distress Syndrome (ARDS)
85. Pneumothorax
86. Pseudoaneurysm
87. Pulmonary edema
88. Heart failure
89. Pulmonary embolism
90. Pulmonary hypertension
91. Pulmonary toxicity, like acute pulmonary syndrome
92. Pulmonary vein dissection
93. Pulmonary vein Stenosis
94. Pulmonary vein thrombus
95. Pump failure
96. Renal failure
97. Respiratory depression
98. Respiratory failure
99. Retroperitoneal hematoma
100. Rhabdomyolysis, including produced by body position or propofol
101. Sedation induced CO2 retention with lethargy and cholecystitis
102. Seizure
103. Sepsis
104. Skin burns (due to cardioversion, tape, etc.)
105. Skin discoloration
106. Skin injury / muscle or connective tissue injury due to body position, electrical cardioversion
107. Skin rash
108. Thrombocytopenia
109. Thromboembolism
110. Thrombosis
111. Thyroid disorders
112. Transient extremity numbness
113. Extremity numbness
114. Transient ischemic attack (TIA)
115. Unintended complete or incomplete AV, Sinus node, or other heart block or damage
116. Urinary retention
117. Urinary tract infection
118. Urinary tract injury or infection related to the urinary catheter
119. Vagal Nerve injury

Anticipated Adverse Events
120. Valvular damage/insufficiency
121. Vasovagal reactions
122. Vision change
123. Volume overload
124. Worsening obstructive, restrictive, or other form of pulmonary disease
125. X-ray radiation injury of skin, muscle and/or organ

14.6 Unanticipated Serious Adverse Device Effect

A (serious) adverse device effect (SADE) is any (serious) adverse effect on subjects' health, safety, rights, welfare, and life-threatening problems including death, which is caused by, or associated with the study device. Accordingly, relationship to device or study is crucial assessment by investigators. An unanticipated adverse device effect (UADE) or unanticipated serious adverse device effect (USADE) is any ADE or SADE that has not been previously identified in nature, severity, or degree of incidence in the study plan or risk analysis report. An investigator shall submit to the reviewing IRB/EC a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but no later than 10 working days after the investigator first learns of the effect, where applicable.

14.7 Clinical Investigation Device Failure/Malfunction/Deficiency

A device has failed if it does not perform according to the instructions for use 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 CRF and **the device must be promptly returned** according to the Sponsor's instructions. If the device failure is associated with an AE, **both** the device failure and AE must be reported to the Sponsor **immediately** upon awareness (refer to section 14.8).

14.8 Reporting Requirements

All serious AEs, UADE/SADE/USADE, and Study device failure/malfunction/deficiency, whether or not they are related to the device or procedure, **must be reported by eCRF** to the Sponsor (**Biosense Webster Clinical Operations)**.

The sponsor is responsible for reviewing AEs (causality, classification, seriousness…) and for ongoing safety evaluations in accordance with the study safety management plan. In case of disagreement between the sponsor and the principal investigator(s) that remain after query resolution, 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, probably device-

related, or possibly device-related) in accordance with relevant regulations and current company procedures.

In the case of serious adverse 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 preventive action is required.

Timing for reporting the different types of AEs is described in Table 14.8A

Table 14.8A Adverse Event Reporting Requirements

Type of Adverse Event	Reporting Requirements
Serious Adverse Events	Report to Sponsor as soon as possible but no later than 72 hours upon awareness of the event
UADE, USADE & SADE	Report to Sponsor as soon as possible but no later than 72 hours upon awareness of the event
Study device deficiency associated with an AE	Report both study device deficiency and AE to Sponsor as soon as possible but no later than 72 hours upon awareness of the event
All other Adverse Events	Routine reporting via eCRF as soon as possible but no later than 2 weeks upon awareness of the event

14.9 Intensity or Severity

Intensity (or severity) of AEs is defined as follows:

Table 14.9A: Intensity or Severity Definitions

Mild	Events that result in minimal transient impairment of a body function or damage to a body structure, and/or does not require intervention other than monitoring.
Moderate	Events that result in moderate transient impairment of a body function or damage to a body structure, or that require intervention, such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure.
Severe	Events that are life threatening and/or result in permanent impairment of body functions or damage to body structures, or that require significant intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure.

Intermittent AEs should be classified according to their greatest severity. A continuous AE that changes severity should be reported as a new AE.

14.10 Outcome

AE outcomes are assessed according to the following classifications:

Table 14.10A: Adverse Event Outcome Classifications

Recovered/ Resolved without Sequelae	Subject fully recovered with no observable residual effects.
Recovering/ Resolving	Subject's condition is improving but residual effects remain.
Recovered/ Resolved with Sequelae	Subject recovered with observable residual effects.
Not recovered/ resolved	AE is ongoing without improvement in overall condition
Fatal	Subject died as a result of the adverse event, whether or not the AE is related to the device or procedure. Note; deaths from any cause occurring on this study are to follow expedited reporting.
Unknown	AE outcome is unknown (e.g., subject lost to follow-up)

14.11 Causality

Cause of AEs is defined as follows:

Table 14.11A: Adverse Event Causality Classifications

Caused By	Relation	Definition of Relation
Device	Definitely (Causal Relationship)	The event is associated with the investigational device beyond reasonable doubt
	Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained
	Possibly	The relationship with the use of the investigational device is weak but cannot be ruled out completely
	Unlikely	The relationship with the use of the investigational device 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 investigational device can be excluded
Study Procedure	Definitely (Causal Relationship)	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

14.12 Documentation

All AEs must be documented on the appropriate eCRF. All AEs must be monitored until they are adequately resolved or stabilized, with follow-up reports submitted to the Sponsor or designee as soon as new information becomes available. Additional documentation may be requested by the Sponsor or designee, such as a written event narrative detailing the clinical course, copies of correspondence with the local IRB/EC, hospital records, death certificates, and autopsy reports, if applicable. Follow-up information 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.

14.13 Safety Oversight

Safety oversight will be conducted as described in the Safety Management Plan. Aggregate safety data will be reviewed regularly throughout the course of the study by the study safety lead or designee to promptly identify new issues or trends which may have an impact on the conduct of the study and/or subject safety.

14.14 Clinical Events Committee (CEC)

Primary Adverse Events will be submitted to the independent Clinical Events Committee (CEC) for review.

15.0 DEVIATIONS FROM PROTOCOL AND GOOD CLINICAL PRACTICE

The investigator is responsible for ensuring that the clinical investigation is conducted in accordance with the procedures described in this protocol except in medical emergencies. 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 may require reporting to the IRB/EC and/or regulatory authority per IRB/EC/regulatory authority requirements.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of a subject may proceed. Such deviations shall be documented as protocol deviations in the eCRF and reported to the IRB/EC/regulatory authority as required.

In emergencies, prior approval for a protocol deviation will not be required, but the Biosense Webster clinical operations personnel should be notified as soon as possible. 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 IRB/EC requirements, failure to report. IRB/REBs must also be notified promptly of significant protocol deviations as they are defined by the IRB/REBs.

16.0 DEVICE ACCOUNTABILITY

16.1 Device Accountability

The Sponsor will keep records of all investigational devices shipped to 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, and disposition information regarding return to the Sponsor. The Sponsor will label all devices as "Investigational device" (as applicable for the region) in a prominent location. All system installations will be performed by trained field services personnel according to internal processes.

The site Device Accountability Log will include the following information:

- Date of receipt
- Individual acknowledging receipt
- Quantity received
- Packing Slip Verification
- Catalog number for catheters
- Serial/lot numbers
- Expiry Date
- Dates devices were used
- Subject IDs for whom devices were used
- Dates of return (as applicable)
- Type of disposal (i.e., return to Sponsor for adverse event, complaint, expired, end of study, etc.)

16.2 Device Returns

All study devices will be labeled "**Investigational Device**" and are only to be used for subjects enrolled in this clinical study.

The allowable equipment for use in the study are those listed in the Study Protocol Section 11.5.

Devices suspected of deficiency or device associated with a (device related or possibly related) adverse event should be returned immediately to BWI and will undergo thorough analysis. Device replacement at the site, except for disposable or resterilizable devices which are replaced according to the respective IFU's, will be performed by trained field services personnel according to internal processes. Returned devices must be decontaminated per hospital policy and labeled with the following:

- Subject identification number, or if unused, site number
- Date of use/event or if applicable, specify "unused"
- Return type (device deficiency related, AE related, etc.)

All tracking information must be retained. All study devices must be returned to:

Complaints Lab
Biosense Webster, Inc.

17.0 MONITORING THE STUDY

Clinical site 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 will undergo periodic monitoring of the study, which involves a visit from a trained Sponsor representative. Monitoring visits may include, but will not be limited to, the following:

- Adherence of the protocol
- Verification of accuracy of study logs such as the Delegation of Responsibility, etc.
- Verification that informed consent is obtained for all subjects participating in the study in accordance with requirements described in the study protocol
- Verification of completeness of the Regulatory Binder.
- Source data verification with the eCRFs.
- Identification and action to resolve any issues or problems with the study.

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

Monitoring activities will be documented through such means as contact reports and follow-up summaries of status and action items. Further details on clinical monitoring are provided in the study specific monitoring plan.

17.1 Early Termination Monitoring Visit

If early termination of the study is required, each site will undergo a monitoring visit as described in the monitoring plan 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. Subjects will be notified of the termination of the study. Any enrolled subjects will continue to be followed per the study protocol requirements until a study closeout plan is implemented that outlines alternative follow-up procedures.

18.0 STATISTICAL ANALYSIS METHODS

18.1 Study Design

Prospective, multicenter, non-randomized, clinical evaluation of the QDOT MICRO™ catheter compared to a historical control performance goal. There are two study arms for the treatment; Main Study, QDOT MICRO™ catheter with constant flow rate (8 mL/min) during QMODE+ RF application and second (variable flow) study, variable flow rate (4-15 ml/min) during QMODE+ RF application. QMODE RF applications will use the same flow rates for both studies.

The tral will enroll **185** evaluable subjects in the Main study and 92 subjects in the second (variable flow) study for a total of 277 subjects. The analysis for the Main study is a standalone analysis and it is not dependent on data from the variable flow study. The results from the variable flow study will only be used for additional claims.

18.2 Treatment Assignment

The treatment assigned for both studies is the QDOT MICRO™ catheter. The difference in the 2 studies is the irrigation flow rate during QMODE+ RF application; Main study irrigation flow rate is 8 mL/min constant and the second study is variable flow of 4-15 mL/min (dependent on catheter tip temperature).

Enrollment into the two studies will be in a sequential fashion. The first 185 subjects will be enrolled in the Main study. Subjects enrolling after the completion of enrollment in the Main study will be enrolled into the second (variable flow) study.

18.3 Interval Windows

Refer to section 13.7 and Table 13.8A.

18.4 Primary and Secondary Endpoint(s), and Associated Hypotheses

The primary goal of the trial is to demonstrate safety and effectiveness. For each study to be successful, both safety and effectiveness endpoints must be statistically significant relative to their respective performance goals.

Study Success

The study will be considered successful if the primary endpoints are met for main study. If the main study is not successful, the data for the second (variable flow) study will not

be submitted for labeling. The second (variable flow) study will be considered successful if both the primary safety and primary effectiveness performance goals are met.

18.4.1 Primary Endpoint(s) and Associated Hypotheses

Acute Safety: The primary safety endpoint is the proportion of subjects with any Primary Adverse Event occurring within 7 days of ablation procedure. The PAE rate will be compared against an PG of 14%.

The primary safety endpoint will be assessed by testing the hypotheses:

$$H_0: p_S \geq 0.14 \qquad \text{vs.} \qquad H_A: p_S < 0.14,$$

where p_S is the proportion of patients with PAE at early onset (within 7 days of ablation procedure).

The primary safety analysis will be performed at the time of the interim analysis for the Main study. In the variable flow study, the primary endpoints will be evaluated after full 12-month follow-up is completed on all subjects.

12-Month Chronic Effectiveness: The primary effectiveness endpoint is the proportion of patients that are free from documented atrial arrhythmia (atrial fibrillation (AF), atrial tachycardia (AT), or atrial flutter (AFL)) episodes at Month 12 (that is, during the 9-month post-blanking period, i.e. Day 91-365).

The primary effectiveness endpoint will be assessed by testing the hypotheses:

$$H_0: p_E \leq 0.50 \qquad \text{vs.} \qquad H_A: p_E > 0.50,$$

where p_E is the proportion of patients that are free from AF, AT, and AFL episodes at 12-month follow-up (includes a 3-month blanking period).

In case early success is achieved, the study will continue to follow up the subjects for the full follow-up duration. The primary effectiveness endpoints based on full 12-month follow-up data will be descriptively summarized in subjects in the PP population. The primary effectiveness endpoint in the variable flow study will be evaluated at the end of the study, i.e. completion of 12-month follow-up in all subjects.

18.4.2 Secondary Endpoints and Associated Hypotheses

No formal statistical hypothesis and inferential statistics will be formulated and performed for the secondary safety and effectiveness endpoints.

Refer to Section 8.2.3.1 for secondary safety endpoint, and Section 8.2.3.2 for secondary effectiveness endpoints.

18.4.3 Other Endpoints

No formal statistical hypothesis and inferential statistics will be formulated and performed for the additional safety and effectiveness endpoints.

Refer to Section 8.2.3.3 for additional endpoints.

18.5 Levels of Significance

The type I error for the interim and final analyses of the primary endpoints for the main study is controlled at one-sided 2.5%. Two-sided 95% confidence intervals will be presented around the percentages unless otherwise specified. For the variable flow study, both primary endpoints will be tested at the end of the study at the 2.5% significance level, and all confidence intervals will be presented at the 95% confidence level unless otherwise specified.

18.6 Analysis Set

The treatment for both studies is the QDOT Micro Catheter, there for the analyses sets are defined identically for both studies.

Safety Population (SP) : The Safety population will include all enrolled subjects who have the investigational device inserted, regardless if RF energy is delivered.

Modified Intent-To-Treat (mITT) Population: the modified Intent-To-Treat (mITT) population will consist of all enrolled subjects who have the investigational device inserted AND meet all eligibility criteria..

Per Protocol (PP) Population: The PP population will include subjects who satisfy the following criteria:

- are enrolled and meet all eligibility criteria
- have undergone RF ablation
- are treated with the study catheters, and have been treated for the study-related arrhythmia

CT/MRA (CTS) Population: The CT/MRA set will consist of the first 40 subjects who are consecutively enrolled in the main study with 3-month CT/MRA assessment. The subject must have readable outcomes at baseline and 3 months.

18.7 Sample Size Justification

The Main study:

The Final analyses for primary safety and effectiveness endpoints will apply Bayesian methods and use a beta-binomial model after all subjects complete the 12 months

follow-up (assuming early success is not achieved for the primary effectiveness endpoint). Non-informative Beta priors will be used for both safety and effectiveness endpoints. Trial simulations were performed to estimate the power for the success of the safety and effectiveness endpoints. Based on PG of 14% for the primary safety endpoint and PG of 50% for the primary effectiveness endpoint, the sample size of 185 subjects will provide above 80% power to declare success for both endpoints controlling the overall type-I error rate at one-sided 2.5% assuming the true PAE rate is 7% and the true effectiveness failure-free rate is 65%. It is also assumed that there are 5% and 12% dropout rates for the safety and effectiveness endpoints, respectively.

Simulations were also performed to estimate the overall type I error for this study under various hypothetical scenarios. The highest type I error rates were reached in the following two scenarios, including 1) the true primary safety rate was on the decision boundary (i.e. equal to 14%) and the device was assumed to be effective: type I error rate was 0.023, and 2) the true primary effectiveness rate was on the decision boundary (i.e. equal to 50%) and the devices was assumed to be safe: type I error rate was 0.011. As the primary safety or effectiveness moves away from the decision boundary, the overall Type-I error decreases. Therefore, considering all scenarios, the overall type I error for claiming success for both safety and effectiveness was controlled at 2.5%.

Based on the simulation results, the study is adequately powered to meet the primary safety and effectiveness endpoints and Type-I error for the overall trial success is controlled at 2.5%.

The Second (variable flow) Study:

The analyses for primary safety and effectiveness endpoints in the variable flow study will apply Bayesian methods using a beta-binomial model with data borrowing from the Main study using a propensity score-integrated power prior approach. Based on a PG of 14% for the primary safety endpoint and a PG of 50% for the primary effectiveness endpoint, and allowing borrowing up to 91 subjects from QDOT MICRO (IDE # G180176) Main study, the sample size of 92 subjects in the variable flow study provides close to 80% power at a one-sided signficance level of 2.5% to declare success for both the safety and effectiveness endpoints assuming the true PAE rate is 7% and the true effectiveness failure-free rate is 65%. Overall power for the variable flow study is maintained close to 80% when information from at least 80 subjects in the Main study is borrowed. It is also assumed that there are 5% and 12% attrition rates for the safety and effectiveness endpoints in the variable flow study, respectively.

18.8 Data Monitoring Committee

Data Monitoring Committee will be formed for this study and will evaluate data from both studies. An independent statistician will be responsible for conducting the interim analyses and reviewing the results with the designated Data Monitoring Committee

(DMC). The DMC charter will document the role and responsibilities of the committee, Sponsor and the independent statistician.

18.9 Analyses to be Conducted

18.9.1 General Conventions

In general, descriptive statistics will be provided for all primary and secondary safety and effectiveness endpoints and other endpoints as appropriate. For continuous variables, number of subjects/events, mean, standard deviation, median, 25% percentile, 75% percentile, minimum, and maximum will be provided. For categorical variables, frequency and percentage will be presented for each category.

Confidence intervals for binary variables, including the primary outcome variables, will be computed using the exact binomial distribution. Categorical variables will be compared using Chi-square or Fisher's exact test. Continuous variables will be compared using ANOVA or Kruskal-Wallis test.

18.9.2 Disposition of Study Subjects

Disposition and accountability of the study subjects will be summarized and listed.

18.9.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized and listed.

18.9.4 Analysis of Primary Endpoint Analyses

The Main study:

The final analyses for primary safety and effectiveness endpoints in the main study will apply Bayesian methods and use a Beta-Binomial model. A vague Beta(1,1) prior will be used for both safety and effectiveness endpoints.

If the primary safety endpoint is met (at the time of the interim analysis) and early success is achieved for the primary effectiveness endpoint, then the trial will be declared a success. If the safety endpoint is not met the study will be deemed unsuccessful. Under the success scenario, the study will continue to follow up the subjects for the full follow-up duration, and the primary effectiveness endpoint based on full 12-month follow-up data will then be descriptively summarized in subjects in the PP population. If early success is not achieved for the primary effectiveness endpoint, then the final effectiveness analysis for the main study will be based on complete follow-up data for effectiveness endpoint and will use a beta-binomial model.

Primary safety endpoint will be analyzed in the mITT population and primary effectiveness endpoint will be analyzed in the PP population.

Assuming early effectiveness success is not achieved, the trial will be considered a success if BOTH

$$\Pr(p_S < 0.14|y,n) > 0.975$$

AND

$$\Pr(p_E > .50|\, x,n) > 0.9775.$$

These thresholds control the overall Type I error rate for the trial below one-sided 2.5% (see appendix C report for additional discussion of Type I error control).

The Second (variable flow) study:

The analyses for primary safety and effectiveness endpoints in the variable flow study will apply Bayesian methods and use a Beta-Binomial model. A propensity score-integrated power prior approach will be used to borrow data from the Main study for establishing safety and effectiveness of the variable flow study. The borrowing approach follows the method described in Yue, L. et al[59]. The catheter design and the procedure workflow with the exception of the flow rate are identical between the Main study and the variable flow study. Preclinical and bench testing concluded comparable performance of the catheter for constant or variable flow rates. Accordingly, data from up to 91 subjects in the Main study will be borrowed for the variable flow study based on similarity in baseline characteristics. Details on the borrowing approach are defined in SAP for the variable flow study.

The primary safety endpoint will be considered met if

$$\Pr(p_S < 0.14|y,n) > 0.975,$$

and the primary effectiveness endpoint will be considered met if

$$\Pr(p_E > .50|\, x,n) > 0.975.$$

18.9.5 Analyses of Secondary and Additional Endpoints

Secondary and additional endpoints will be analyzed separately in each study. Descriptive statistics will be presented for the secondary safety endpoints in the Safety Population.. Descriptive statistics for the secondary effectiveness endpoints will be analyzed in the PP population. For the Main Study, descriptive statistics for additional endpoints will be analyzed in the Safety Population, particularly, incidence of severe PV stenosis will be analyzed in the CMSP population. All of these analyses will be performed after the 12 months follow up is complete. No formal statistical hypotheses and inferential statistics will be formulated and performed for the secondary and additional effectiveness and safety endpoints. Details of analyses methods for secondary and additional endpoints will be provided in SAP.

18.9.6 Plans for Interim Analysis

One (1) interim analysis per arm is planned for early success claim in the Main study. The details on the timing of the interim analysis are provided in the simulation report and the SAP. For the safety endpoint, the outcome for all patients will be known at the time of the interim analysis in each arm, and therefore, the primary safety analyses will be performed at the time of the interim analyses. Early success will be declared at the interim analysis for the Main study if:

1. The safety objective has already been met, and
2. Posterior probability of the effectiveness proportion p_E being greater than 50% is greater than 0.9975

18.9.7 Handling of Missing Data

Missing data will be queried for reasons and handled on an individual basis.

At the time of early success interim analysis in the Main study (final safety analysis), if a subject's safety follow-up data is missing but a PAE has occurred earlier, then the subject will be considered having an event. If a subject's follow-up data is missing for the 3-month follow-up and the subject has not had a PAE, then that subject will be excluded from the early success safety analysis. For each early success interim analysis of the effectiveness endpoint, the subjects with incomplete follow-up data will be censored at the time of their last follow-up visit, and only their observed partial follow-up time will contribute to estimating model parameters.

For the variable flow study, if a subject is missing 3-month follow-up and the subject has not had a PAE, the subject will be excluded from the primary safety endpoint analysis. Information will not be borrowed from subjects in the Main Study without PAE but were missing 3-month follow-up.

For final effectiveness analysis in the Main Study, if a subject has an effectiveness failure at any time during the evaluation period, then the subject will be considered having an event. Subjects without an effectiveness failure who do not have full 12 months of follow-up will be excluded from the final effectiveness analysis.

For the primary effectiveness endpoint analysis in the variable flow study, if a subject has an effectiveness failure at any time during the evaluation period, then the subject will be considered having an event. Subjects without an effectiveness failure who do not have full 12 months of follow-up will be excluded from the final effectiveness analysis. No information will borrowed from subjects who are failure free in the Main study but do not have full 12-month follow-up.

18.9.8 Sensitivity Analyses

The Main study:

The primary safety endpoint will be analyzed in the Safety Population as sensitivity analyses. The primary effectiveness endpoint will be analyzed in the Safety Population for those subjects who have undergone RF delivery with the study catheter as sensitivity analyses. In addition, tipping point analysis[59] will be performed for the primary effectiveness endpoint in the PP population and for the primary safety endpoint in the mITT population to assess the impact of missing outcomes on study conclusions. These sensitivity analyses will be done after the 12 months follow-up is complete. Additional details will be defined in the SAP for the Main study.

The Variable Flow study:
Details are defined in the SAP for the variable flow study.

18.9.9 Subgroup Analyses

For the Main study, subgroup analyses for the primary endpoints and acute effectiveness endpoints will be performed after the 12 months follow-up is complete, including but not limited to: age, gender, ablation mode, individual site, CF and ablation index etc. PP population will be used for primary effectiveness endpoint and Safety population will be used for primary safety endpoint for the subgroup analyses. Details of analyses methods will be defined in the SAP.
Ablation mode subgroups:

- Set 1- QMODE+ alone for PVI, QMODE+ & QMODE for PVI, QMODE alone for PVI;
- Set 2- QMODE+ alone for index procedure, QMODE+ & QMODE for index procedure, QMODE alone for index procedure

18.9.10 Assessment of Site Homogeneity

For the Main study, there will be up to 30 sites recruiting the approximate 185 subjects in US.

Each site should enroll no more than 15% of the total enrollment in each study to minimize the possibility that the study results could be highly influenced by a few sites. Sites with less than five subjects will be combined according to geographic regions. Using this pre-determined criterion, sites with less than five subjects within the same geographic region will be combined such that the combined center(s) would have five or more subjects and no more than 5 sites combined.

Chi-square test will be used to examine the homogeneity across sites for the primary effectiveness and safety endpoints using data from the patients in the Main study. A p-value less than 0.15 will be considered statistically significant for an assessment of

homogeneity across sites. A non-significant result will support pooling of sites for the primary analyses.

If the sites are not poolable, logistic regression models treating site as a random effect will be fit to examine the impact of site heterogeneity on the primary endpoints. The claim of trial success will be based upon the totality of the data.

19.0 ETHICS AND PROTECTION OF HUMAN SUBJECTS

19.1 Ethics Review

Study materials including informed consent must be reviewed and approved by an appropriately-constituted IRB/IEC/REB before enrollment of subjects. Biosense Webster and the IRB must approve in writing any changes to the protocol.

Proof of IRB/IEC/REB review and approval must be obtained prior to subject enrollment. Investigators are responsible for submitting and obtaining initial and continuing review (per local regulations) of the study by their IRB/IEC/REB.

19.2 Patient Informed Consent

Biosense Webster and the reviewing IRB/IEC/REB must approve any modifications to the ICF or PI/ICF. The ICF may be translated as appropriate. Certification of accurate translation will be required.

Informed consent is mandatory and must be obtained from all subjects prior to their participation in this study. Copies of all signed consents must be retained in the records of the study, and an unsigned sample copy of the approved ICF must also be in the study file. Subjects must each receive a copy of the ICF.

19.3 Confidentiality

All information and data sent to Biosense Webster concerning subjects or their participation in this study will be considered confidential. Only authorized Biosense Webster personnel or representatives, or representatives of Health Authorities (HA) or Regulatory Authorities (RA) acting in their official capacities will have access to these confidential files. No data transmitted to Sponsor for evaluation and reporting will contain identifiable references to individual subjects.

19.4 Subject Confidentiality/Record

All representatives of the Sponsor have undergone training for Privacy regulations and appropriate conduct for their compliance. For the duration of this study, all representatives of the Sponsor will comply with all privacy regulations regarding contact with subjects, their medical record information, copying of information, protection of the subject identities, and other aspects. Authorization for limited access to Protected Health Information by Sponsor personnel will be obtained as part of subject informed consent.

Site personnel should also be attentive to privacy considerations and should not transmit PHI outside of PI control (e.g., via .pdf or FAX) without redaction of patient identifiers.

Privacy considerations such as above will also be covered in protocol training for both Sponsor representatives and study site personnel.

20.0 DATA MANAGEMENT

The Sponsor will be responsible for all data management activities. These activities include development of a database, utilizing validated database software, into which all study data will be entered by the clinical sites. The Sponsor will be responsible for ensuring the overall integrity of the database.

20.1 Electronic Case Report Forms (CRFs)

Electronic CRFs will be used to collect all subject data during the study.

Electronic CRFs (eCRFs) have been developed to capture the information outlined in this Study Protocol. Data on these eCRFs will be monitored, corrected if necessary, and entered into a validated database. All changes made to the data will be tracked in the electronic audit trail, recording the current value, previous value, reason for change, date timestamp of data entry/change, and the name of the person who changed the data. The investigator will electronically sign all subject eCRFs as verification that the data have been reviewed and correctly reflects source documentation. Data from these eCRFs will be used to provide analysis of this study.

20.2 Data Reporting

The investigator, or a designated individual, is responsible for recording data from the trial on the eCRFs supplied by Biosense Webster. The investigator or a delegated individual is required to electronically sign eCRFs on the appropriate pages to verify that he/she has reviewed and attests to the correctness of the recorded data. Completed eCRFs will be reviewed and monitored remotely and at the research site by Biosense Webster personnel or designees throughout the trial. To this end, the investigator and institution must permit inspection of trial files including original (source) records and subject eCRFs by sponsor representatives and responsible government agencies.

Table 20.2A. 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 IRB/EC approval	Biosense Webster	Should report within 5 working days
Final report	Biosense Webster, IRB/EC	Will prepare a final report separately for the main study and the variable flow study for the clinical investigation as required per national regulations.

Informed consent not obtained from subject	Biosense Webster, IRB/EC (per IRB/EC requirements)	Should report within 5 working days

20.3 Data 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 points will be queried as necessary throughout the trial. Biosense Webster may request further documentation such as physician and/or cardiac EP lab procedure notes when complications or device deficiencies are observed and reported. Biosense Webster will be responsible for auditing the database and confirming the overall integrity of the data.

20.4 Procedural Data

It is the responsibility of the investigator to provide timely completion of CRFs to the sponsor.

20.5 Source Documentation

Data entered into the eCRFs may be taken from source documentation, such as hospital procedure reports, admission and discharge summaries, and other hospital or physician office/clinic documents. If no standard hospital or office document exists to capture some of the information that may be unique to this study, a worksheet may be developed to record this information. Data collection instruments should clearly identify the individual collecting the data and the date of collection. The instrument of original capture of all study data will serve as the source document for future verification of for those data parameters. Privacy regulations will be observed during the use of these source documents during monitoring.

21.0 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 investigational 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.

22.0 ADMINISTRATIVE RESPONSIBILITIES

22.1 Records and Reports

22.1.1 Records

Records to be maintained by the investigator include:

- Study protocol and all amendments with signature pages
- Signed clinical study agreement and Statement of Investigator
- IRB/IEC/REB approval letter, including approved ICF document
- Evidence of IRB/IEC/REB compliance
- Other significant IRB/IEC/REB correspondence
- Significant sponsor correspondence relating to the study
- CVs for all investigator(s)
- Financial Disclosure for key study staff
- Records of protocol and supporting training
- Site personnel delegation of authority/responsibility
- Clinical Monitor/Site Visit sign-in log
- Device accountability log
- Reports (e.g. annual reports, final reports from investigator and Sponsor)

The following records must be maintained for each subject enrolled in the study:

- Signed Patient ICF
- All completed electronic CRFs and supporting source documentation
- Supporting documentation of any AEs and/or death

The investigator must retain copies of procedure reports, procedure nursing notes and the results of any interventional procedures that occur while the subject is enrolled in the study. Biosense Webster reserves the right to secure data clarification and additional medical documentation on subjects enrolled in this study.

22.1.2 Record Retention

Records and reports of the study will remain on file at sites for a minimum of two (2) years after its completion/termination. Records for U.S. sites must be maintained in accordance with 21 CFR 812.140 [d], and for OUS sites, according to local requirements.

If the principal investigator plans to leave the study site, he/she is responsible for identification of another individual at site who will assume the obligation for file

maintenance and management of any continuing subjects. Biosense Webster and pertinent HA/RA, per its requirements, should be notified of this change.

Records and reports may be discarded upon notification by Biosense Webster to the study site. Site personnel should contact Biosense Webster prior to destruction of any study-related records and reports to ensure appropriate record retention.

22.1.3 Investigator's Final Report

Upon completion or termination of the Biosense Webster study, the principal investigator must submit a final written report to the approving Investigational Review Board/Ethics Committee (as required by the IRB/IEC/REB) and provide a copy to Biosense Webster. The report should contain the information required by the IRB/IEC/REB and be submitted in the time frame required by the IRB/IEC/REB.

23.0 TERMINATION OF THE STUDY

The study may be suspended or terminated early at the discretion of the Sponsor, for reasons such as incidence of unanticipated serious adverse device effects that may pose a risk to other subjects. In any early termination, already enrolled subjects will continue to be followed per the study protocol requirements.

Sponsor may also terminate a site prior to completion if it believes the site is no longer capable of participating (e.g., cannot fulfill subject enrollment or protocol compliance goals, site suspension by IRB/REB).

At termination of the investigation, each active site will undergo closeout monitoring to conclude any outstanding issues, resolve all data discrepancies and make sure any outstanding eCRFs are completed, discuss responsibilities with the Principal Investigator, and discuss any other items relevant to the conclusion of the study. The termination process will be documented by a written report.

24.0 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, investigational medical device, 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.

25.0 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.

26.0 REFERENCES:

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27.0 APPENDIX A: STUDY DEFINITIONS

Term	Definition
Adverse Event (AE)	Any unfavorable and unintended sign, medical occurrence, disease or injury (including abnormal laboratory findings) in subjects, users or other persons temporally associated with the use of a medicinal product or device whether or not related to the sponsor's product. This definition includes events related to the medical device and/or the comparator, and events related to the procedure in which the device was used.
Adverse Device Effects (ADE's)	Adverse events related to the use of the medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use deployment, implantation, installation, or operation, or any malfunction of the medical device. This definition includes any event resulting from use errors or from intentional misuse of the investigation medical device.
AF/AT/AFL Episode	An episode of AF/AT/AFL ≥ 30 seconds in duration.
AF Episode	An atrial fibrillation episode is defined as AF which is documented by ECG monitoring and has a duration of at least 30 seconds, or if less than 30 seconds, is present continuously throughout the ECG monitoring tracing. The presence of subsequent episodes of AF requires that sinus rhythm be documented by ECG monitoring between AF episodes
Anticipated AE	An effect which by its nature, incidence, severity or outcome has been identified as possible complications associated with the medical device and/ or intervention procedure.
Atypical Flutter	Macro-reentrant circuits within the atria where activation rotates around large obstacles that does not meet the criteria for Typical Flutter.

Term	Definition
Bleeding Complications (ISTH definition):	Major (ISTH definition): Fatal bleeding AND/OR symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome AND/OR bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of blood. Clinically relevant nonmajor bleed (ISTH definition): An acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response such that it leads to one of the following: hospital admission for bleeding; physician guided medical or surgical treatment for bleeding; change in antithrombotic therapy (including interruption or discontinuation). Minor bleeding (ISTH definition): All nonmajor bleeds. Minor bleeds are further divided into clinically relevant and not.
Catheter Insertion	Defined as the QDOT MICRO™ catheter breaching the sheath and entering the bloodstream.
Device Deficiency	Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction (failure of a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or protocol), misuse or use error and inadequate labeling.
Documented AF/AT/AFL episode	An AF/AT/AFL episode documented by an electrocardiographic monitoring tool. This may include ILR, ECG, TTM, Holter monitor, or telemetry strip. Reporting of a symptomatic episode by a patient or in a referral letter is not considered a documented AF episode.
Minor Pericarditis	**Pericarditis will be considered 'minor if is treated using only analgesics and does not extend hospitalization by more than 48 hours.**
Paroxysmal AF	Paroxysmal AF is defined as recurrent AF (≥ 2 episodes) that terminates spontaneously within 7 days. Episodes of AF of ≤ 48 hours duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes.
Permanent AF	Not appropriate in the context of patients undergoing catheter ablation of AF; refers to a group of patients where a decision has been made not to pursue restoration of sinus rhythm by any means, including catheter or surgical ablation.
Persistent AF (PsAF)	Persistent AF is defined as continuous AF that is sustained beyond 7 days and less than 1 year.

Term	Definition
Serious adverse event (SAE)	1. Any adverse event that: • Led to a death • Led to a serious deterioration in health that either: o Resulted in a life-threatening illness or injury, or o Resulted in a permanent impairment of a body structure or a body function, or o Required in-patient hospitalization or prolongation of existing hospitalization, or o Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death or a congenital abnormality or birth defect 2. Any Device Deficiency that could have led to an SAE A planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.
Serious Adverse Device Effects (SADE's)	Adverse device effects that has resulted in any of the consequences characteristic of a serious adverse event.
Symptomatic AF/AT/AFL Episode	Symptom(s) which is/are exhibited by the subject which made them seek medical attention and are concurrent with a documented episode of AF/AT/AFL by either ECG, TTM, Holter monitor, or telemetry recording. Symptoms may include but are not limited to: palpitations, irregular pulse (e.g., rapid, racing, pounding, fluttering, bradycardia), dizziness, weakness, chest discomfort, and breathlessness.
Typical Flutter	Atrial flutter is caused by a reentrant rhythm in either the right or left atrium. Typically initiated by a premature electrical impulse arising in the atria, atrial flutter is propagated due to differences in refractory periods of atrial tissue. This creates electrical activity that moves in a localized self-perpetuating loop. For each cycle around the loop, there results an electric impulse that propagates through the atria.

Term	Definition
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated SADE: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report
Ventricular Tachycardia (VT)	Ventricular tachycardia: a tachycardia (rate $\geq$ 100/min) with three or more consecutive beats that originates from the ventricles independent of atrial or AV nodal conduction. Continuous VT for $\geq$ 30 s or that requires an intervention for termination (such as cardioversion).

28.0 APPENDIX B: QMODE

Introduction QMODE Temperature Control Mode

The QDOT MICRO™ catheter with QMODE introduces temperature controlled ablation to irrigated catheters. Temperature controlled ablation allows RF power to be delivered safely without tip char or steam pops. The QMODE temperature control mode utilizes the temperature sensing capabilities of the QDOT MICRO™ catheter to optimize power delivery ensuring efficient ablation. When using the QMODE temperature control mode the irrigation rate will vary based on temperature to both cool the catheter tip adequately and retain temperature sensitivity, ensuring the safety profile.

The QMODE temperature control is designed to maximize RF lesion efficiency by using temperature feedback from the tip to adjust power and irrigation flow. The QMODE temperature control mode monitors the temperature rate of change in relationship to the set target temperature during RF application. To maintain a desired power levels at a safe temperature, the algorithm applies an accurate correction to control the irrigation flow rate.

- For maximum power settings, 35W or lower: The flow rate starts at low flow (4ml, lowest setting) to increase temperature sensitivity. If the set power is titrated down because the temperature exceeds the set target temperature (50°C), the generator changes the pump flow rate from low (4mL) to high flow (15 mL) to maintain the set maximum power. Once the temperature decreases the pump irrigation flow rate is returned to low (4mL).

- For maximum power settings, greater than 35W: The flow rate starts at high flow (15ml) for safety. If the temperature drops below the set maximum low flow temperature (45°C), the generator changes the pump from high (15 mL) to low (4mL) flow. The change to low flow allows the temperature to rise above the set maximum low flow temperature and closer to the target temperature.

28.1 Use of the QDOT MICRO™ QMODE algorithm

In the event of spontaneous or induced AF and/or atrial flutter, the placement of additional RF lesions outside of the PV ostia in Qmode is at the discretion of the investigator and includes the following:

- Linear lesions between both superior PVs (roof line), the mitral annulus and the left inferior PV (mitral isthmus line) or between the LA roof and mitral annulus (anterior line)
- Ablation for any non-PV foci in the LA and/or RA, including isolation of the superior vena cava (SVC)
- Linear lesions in the cavo-tricuspid isthmus

If linear lesions are placed, it is recommended that complete conduction block across the ablation line be demonstrated by mapping and/or pacing maneuvers.

28.2 Recommended ablation parameters

QMODE temperature control mode will be used for PVI once the investigator deems QMODE+ unable to complete PVI. Additionally, QMODE temperature control mode will be used for all RF applications outside the PV ostia during the study ablation procedure (refer to Sections 13.3.4 and 13.3.5).

The QDOT MICRO™ catheter with QMODE temperature control mode is designed to maximize RF lesion efficiency by using temperature feedback from the tip to adjust power and irrigation flow. For power levels from 1-50W, the generator changes the pump irrigation flow rate from low (4 mL/min) to high flow (15 mL/min) or from high to low flow to reach and maintain the set maximum power without exceeding the set target temperature (50°C). The QMODE temperature control mode minimizes the irrigation rate thus increasing temperature sensitivity at the catheter tip.

Table 28.2A: QMODE Ablation parameters

Power	Target Temp*		Cut-off Temp		Nominal Irrigation Flow rate
	Range	Recommended	Range	Recommended	
25-35 W	45-50ºC	50ºC	50-55ºC	55ºC	4mL**
36-50W***	45-50ºC	50ºC	50-55ºC	55ºC	15mL**

* 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 30 sec.

Note: The default parameters for QMODE temperature control are user-adjustable, in case the investigator deems appropriate.

Recommendation for CoolFlow® Irrigation Pump Setting and RF Power-delivery

The CoolFlow® Irrigation Pump will deliver a continuous infusion of 2 ml/min of room temperature heparinized saline (1 u heparin/1 ml saline) when not delivering RF energy. Increase the irrigation to high flow rate starting up to minimal 2 seconds before the onset of RF energy delivery and maintaining this higher flow rate up to 5 seconds after termination of the energy application.

QMODE Contact Force (CF) Settings

When using the study catheter in QMODE the recommended Contact Force working range should be between 5 and 30g.

Visitag Settings (recommendation)

It is recommended that ACCURESP™ be enabled; Respiratory Gating Mandatory (unless using Jet Ventilation)

- Stability Settings:
  - Range: 3 mm
  - Time: 3 seconds
- Filter (FOT) Settings:
  - If an FOT filter is desired, the percentage of time of the chosen gram force is recommended to be set on 50%

Recommended Temperature Range and RF Power Settings

- QMODE Temperature settings
  - Below or equal to 35 W
    - Temperature Cut-Off: 55°C
    - Target Temperature: 50°C
  - Above 35W
    - Temperature Cut-Off: 55°C
    - Target Temperature: 50°C (prevents overheating)

Note: The default parameters are user-adjustable, in case the investigator deems appropriate.

QMODE Ablation Workflow:

- If the temperature increases rapidly, stop RF application immediately
- RF power range of 15-50 Watts (W) is recommended for atrial ablation
- At anatomical locations, not on the LA posterior wall or CS:
  - Maximum allowed power should not exceed 50 W
  - Duration of ablation should not exceed 60 seconds of continuous ablation at a given location
- Move/drag the catheter to a new location when clinically effective ablation is achieved (EGM reduction and/or impedance drop).
- Duration of ablation as well as 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.

Precautions while ablating on the Posterior wall and Coronary Sinus:

- LA posterior wall and close to the esophagus:
  - Start ablation using standard workflow for posterior wall.
  - Move/drag the catheter to a new location if clinically effective ablation is achieved within 20 seconds (EGM reduction and/or impedance drop).
  - Maximum power used SHOULD NOT exceed 35 W.
  - Duration of ablation as well as the decision to interrupt RF power delivery at any time during ablation SHOULD be guided by:
    - Clinical Investigator judgment and monitoring of ablation effectiveness parameters commonly used such as EGM reduction and/or impedance changes
    - Esophageal temperature changes should be monitored by an endo-luminal esophageal probe or method used to move esophagus as needed (refer to)
    - Duration of ablation should not exceed 30 seconds on posterior wall.

- Ablation within the Coronary Sinus (CS):
  - A maximum of 35 W will be used if ablation is required in the CS
  - Duration of ablation is limited to 20 seconds per ablation location in the CS

29.0 APPENDIX C: JUSTIFICATION OF SAFETY PERFORMANCE GOAL

In a recent BWI study (Heliostar), the FDA had recommended using a meta-analysis for combining safety rates from relevant studies for deriving a performance goal. For this recent study, the agency had agreed to setting the performance goal by allowing a 50% increase in risk from the upper bound of the 95% confidence interval for the combined safety rate.

Data from recent clinical trials for devices similar to the device in the current study were reviewed as a first step to deriving the performance goal for the safety endpoint. The following trials were reviewed: TOCCASTAR, ZERO-AF, and SMART-AF. A meta-analysis approach was taken to estimate the average composite endpoint rate. Since the definition of the safety composite varies across the studies reviewed, individual complication rates were reviewed and utilized to derive composite rates from each trial that are more closely aligned with the proposed endpoint definition. Table 1 summarizes the event rates as observed in each of the trials.

Table 1: Observed event rates

	TactiCath™ CF (n=152)	**TactiCath™ TC (n=143)**	**Zero AF Blazer Open-Irrigated (n=157)**	**Zero AF Thermocool (n=164)**	**Smart AF (n=161)**
Design	**RCT**		**RCT**		**Single**
Device /Procedure Death					
Atrial esophageal fistula					
Myocardial Infarction			1 (0.6%)	0 (0.0%)	
Cardiac tamponade/ Perforation	1 (0.66%)	1 (0.70%)	4 (2.5%)	3 (1.8%)	4 (2.5%)
Thromboembolism			1 (0.6%)	0 (0.0%)	
Stroke/CVA					
TIA					
Phrenic nerve paralysis					
PV Stenosis	0 (0.0%)	1 (0.7%)	1 (0.6%)	2 (1.2%)	
Major Vascular Access/ Bleeding Complication			2 (1.3%)	2 (1.2%)	3 (1.86%)
Pulmonary or bronchial complication			5 (3.2%)	4 (2.4%)	
Pericarditis	2 (1.3%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	2 (1.24%)
Hospitalization					6 (3.72%)
Heart Block					1 (0.62%)
Pericardial Effusion					1 (0.62%)
AF or AFL requiring cardioversion (12M)					
Atrial arrhythmia			1 (0.6%)	1 (0.6%)	
All cause death			1 (0.6%)	1 (0.6%)	
Events*					**17**
Subject level rate	**3 (1.97%)**	**2 (1.4%)**	**16 (10.2%)**	**13 (7.9%)**	**16 (9.9%)**

***** Number of events observed if reported**.**

Table 2 summarizes the event rates consistent with the proposed safety composite definition.

Table 2: Observed event rates consistent with the proposed safety composite definition (Translated safety rates)

	TactiCath™ CF (n=152)	TactiCath™ TC (n=143)	Zero AF Blazer Open-Irrigated (n=157)	Zero AF Thermocool (n=164)	Smart AF (n=161)
Design	**RCT**		**RCT**		**Single**
Device / Procedure Death					
Atrial esophageal fistula					
Myocardial Infarction			1 (0.6%)		
Cardiac tamponade/ Perforation	2 (1.3%)	2 (1.4%)	4 (2.5%)	3 (1.8%)	4 (2.5%)
Thromboembolism			1 (0.6%)		
Stroke/CVA					
TIA					
Phrenic nerve paralysis					
PV Stenosis		1 (0.7%)	1 (0.6%)	2 (1.2%)	
Major Vascular Access/Bleeding Complication	3 (2.0%)	3 (2.1%)	2 (1.3%) 1 Hematoma (Ablation procedure) 1 Sanguineous drainage	2 (1.2%) 1 AV fistula 1 Rectus Sheath Hematoma	3 (1.86%)
Pulmonary or bronchial complication	2 (1.3) P. edema	2 (1.4%) P. edema	5 (3.2%) 2 Heart failure / pulmonary edema 3 Pulmonary	4 (2.4%) Pulmonary	
Pericarditis	2 (1.3%)		1 (0.6%)		3 (1.86%)
Heart Block					1 (0.62%)
Event total	**9 (5.9%)**	**8 (5.6%)**	**14 (8.9%)**	**11 (6.7%)**	**11 (6.8%)**
Rate *	**7 (4.6%)**	**8 (5.6%)**			**11 (6.8%)**

*Number of subjects with events if reported.

Figure 1 Meta-analysis results

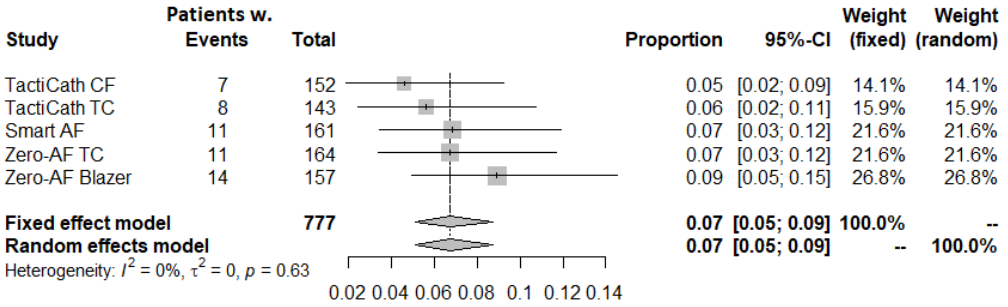

Figure 1 shows the result of the meta-analysis for combining the safety rates. Based on the plot, the upper bound of the 95% confidence interval was estimated to be equal to 9%. The proposed performance goal of 14% would reflect an approximately 50% increase in risk from the upper bound of the 95% CI.

30.0 APPENDIX D ADAPTIVE DESIGN MAIN STUDY

Simulation Report for Q-FFICIENCY Study Main Study

30.1 Introduction

This document describes the single-arm trial design for Biosense Webster's pre-market clinical evaluation of the QDOT MICRO™ Catheter to demonstrate the acute safety and 12-months effectiveness. The trial will enroll N=185 subjects. One interim analysis for early success will be performed at 6 months after the last patient is enrolled.

30.1.1 Endpoints

30.1.1.1 Primary Efficacy Endpoint

The primary effectiveness endpoint is freedom from documented atrial arrhythmia (atrial fibrillation (AF), atrial tachycardia (AT) or atrial flutter (AFL)) episodes at Month 12 (that is, during the 9-month post-blanking period). The proportion of patients that are free from failure at Month 12 will be compared against a performance goal (PG) of 50%.

30.1.1.2 Primary Safety Endpoint

The primary safety endpoint is occurrence of primary adverse events(PAE) within 7 days of an ablation procedure. The PAE rate will be compared against a PG of 14%. PAE includes the following AEs and are defined in the protocol:

- Death
- Atrio-Esophageal Fistula
- Cardiac Tamponade/Perforation
- Myocardial Infarction
- Stroke / Cerebrovascular Accident
- Thromboembolism
- Transient Ischemic Attack
- Diaphragmatic Paralysis
- Pulmonary Vein Stenosis
- Pericarditis
- Vagal Nerve Injury
- Major Vascular Access Complication / Bleeding

30.2 Adaptive Design

30.2.1 Primary Analysis

The primary goal of the trial is to demonstrate effectiveness and safety. For the trial to be successful, both primary safety and effectiveness endpoints must be statistically significant relative to their respective PGs.

The effectiveness endpoint will be assessed by testing the hypotheses (assuming early success for effectiveness is not achieved):

$$H_0: p_E \leq 0.50 \qquad \text{vs.} \qquad H_A: p_E > 0.50,$$

where p_E is the proportion of patients free from effectiveness events.

Let X be the number of patients that are failure-free through 12 months. We model the number of patients free from an event as

$$X \sim \text{Binomial}(n, p_E),$$

where n is the number of patients. We use a vague Beta(1, 1) prior distribution for p_E. Then the posterior distribution is

$$(p_E|x, n) \sim \text{Beta}(1 + x, 1 + n - x).$$

Similarly, the hypothesis test for the safety endpoint is:

$$H_0: p_S \geq 0.14 \qquad \text{vs.} \qquad H_A: p_S < 0.14,$$

where p_S is the 7-day PAE. We model the number of patients with PAEs as

$$Y \sim \text{Binomial}(n, p_S)$$

with a vague Beta(1, 1) prior distribution on p_S.

Assuming early success for effectiveness is not achieved, the trial will be considered a success if BOTH

1. $\Pr(p_E > 0.5|x, n) > 0.9775$ AND
2. $\Pr(p_S < 0.14|y, n) > 0.975$.

These thresholds control the overall Type I error rate for the trial below one-sided 2.5% (see Section 29.5.1 of this report for additional discussion of Type I error control).

30.2.2 Interim Analyses for Early Success

One interim analysis is planned for an early success claim. The interim will occur 6 months after enrollment is complete; that is, 6 months before the final analysis. For the safety endpoint, the outcome for all patients will be known at the time of the interim analysis and therefore the primary safety analysis will be performed at the time of the interim analysis. It should be noted that because these two tests are identical there will not be an increase in type-I error.

At the interim analysis, the trial will declare early success if:

1. The safety objective is met.

2. Posterior probability of the effectiveness proportion p_E being greater than 50% is greater than 0.9975.
3. .

30.2.3 Longitudinal Modeling for Effectiveness

For effectiveness, the time-to-failure during the 9-month(39 weeks) post-blanking period is modeled by using a piecewise exponential model. The model has three distinct time intervals: (0, 2], (2, 8], and (8, 39] weeks. Failure times during each interval is exponentially distributed, with different hazard rates in each segment. The model is:

$$f(t) = \exp(-th(t)),$$

where

$$h(t) = \begin{cases} h_1 & 0 < t \leq 2; \\ h_2 & 2 < t \leq 8; \\ h_3 & 8 < t \leq 39. \end{cases}$$

These intervals are based on a model used in the ThermoCool Pivotal trial. A vague Gamma(1, 1) prior distribution will be used for each h in the model.
Given hazard rates h_1, h_2, and h_3, the failure-free rate at 12 months p_E can then be estimated by

$$p_E = \exp(-[2h_1 + (8-2)h_2 + (39-8)h_3]).$$

At the interim, the total number of primary effectiveness events and the total subject exposure time will be used to update the vague Gamma prior and obtain the posterior Gamma distribution for each segment. Then 10,000 random hazard rates will be sampled from the posterior distribution for each segment and each triplet set of hazard rates will be used to calculate p_E. The distribution of p_E is estimated based on the 10,000 calculated $p_E s$. If the probability of p_E being greater than 50% is greater than 0.9975(99.75%), the trial will declare early success.

30.3 Simulation Scenarios

The operating characteristics of this trial were determined through trial simulation. We hypothesized several scenarios for the underlying rates for the effectiveness and safety endpoints and simulated the entire trial multiple times under each scenario. In each virtual trial, the interim analysis was conducted according to the pre-specified rules, and results were tracked for each trial, including whether the trial was successful on each endpoint individually and on both endpoints, whether trial success was achieved early, etc. This section describes the parameters that were used to simulate subject-level data for the virtual trials.

30.3.1 Effectiveness Profiles

In order to simulate the effectiveness outcome for a virtual subject, we need to simulate whether the subject has a failure and when that failure occurs. As previously discussed in section 29.2.3, a piecewise exponential time-to-failure model is assumed and calibrated to

have a particular failure rate $(1 - p_E)$ at the end of follow-up. The profiles are constructed by taking advantage of the relationship:

$$p_E = \exp(-[2h_1 + (8-2)h_2 + (39-8)h_3]),$$

where p_E is the failure-free rate at 12-months. Previous study of catheter is assumed to estimate the hazard rates for the three pieces. From ThermoCool SSED, the reported hazard rates have the following pattern:

$$h_1 = (38.06)h_3;$$
$$h_2 = (1.71)h_3;$$
$$h_3 = (1)h_3.$$

To simulate data, we use the above multiplicative factors from ThermoCool and then find a value for h_3, such that when multiplied by each of the assumed rates for the three-time intervals, the failure-free rate at 12 months (39 weeks following 13weeks blanking period) matches the desired scenarios. Table 1 shows the derived hazard rates that were used to simulate data for a range of assumed failure-free rates.

Table 1: *Parameters to generate failure times*

	Hazard Rate (h)		
Failure-free Rate	h_1	h_2	h_3
0.50	0.2248	0.0101	0.0059
0.55	0.1938	0.0087	0.0051
0.60	0.1656	0.0074	0.0044
0.65	0.1397	0.0063	0.0037
0.70	0.1157	0.0052	0.0030
0.99	0.0032	0.0001	0.0001

In order to compute the predictive probability of success for the effectiveness endpoint, 2500 imputations were performed for each subject with missing outcome in the simulations

30.3.2 Adverse Event Rate Profiles

The 7-day PAE outcome for each subject is simulated as a Bernoulli random variable, with scenarios defined by the rates shown in Table 2.

Table 2: *Parameters to generate PAE outcomes*

True AE Rate
0.01
0.07

0.08
0.10
0.12
0.14

30.3.3 Enrollment Rates

We simulate three scenarios for the enrollment rate. The "expected" scenario assumes that full enrollment of N=185 would take approximately 7 months on average. The “fast” and "slow" scenarios assume that full enrollment would take, on average, 6 and 8 months respectively. Table 3 shows the rates for each scenario.

Table 3: *Monthly enrollment rates*

	Month							
Rate(patients/month)	1	2	3	4	5	6	7	8
Expected	5	15	25	30	40	40	30	
Fast	5	20	35	45	45	35		
Slow	2	10	20	30	35	35	35	18

30.3.4 Attrition Rate Profile

For each subject, a time-to-withdrawal is simulated from an exponential distribution with a 5% dropout rate for the safety outcome and a 12% dropout rate for the effectiveness outcome. Both dropout rates are per year of follow-up. If a subject experiences a failure prior to their withdrawal time, then their outcome is recorded as a failure. A subject is censored at the time of withdrawal if the simulated withdrawal time is prior to the simulated failure time.

30.4 Operating Characteristics

For the scenarios described above, we simulate multiple virtual trials and track the behavior of each trial, including the final outcome of the trial, whether success was declared early, etc. The results for Type I Error are based on 10,000 simulated virtual trials per scenario. For all other scenarios, 5,000 virtual trials were simulated.

30.4.1 Type I Error Control

This section summarizes the probability of a successful trial under the null hypotheses for both safety and effectiveness. Table 4 summarizes Type I error rates for the trial under various scenarios; that is, the probability of declaring success on both endpoints under two scenarios: (1) Assuming the true failure-free rate is 50% with various range of the true PAE rates; and (2) Assuming the true PAE rate is 14% with various range of the true failure-free rates.

The scenario that is expected to have the largest Type I error rate is either when the true PAE rate is 14% and the device is assumed to be effective (true failure-free rate is 99%) , or when the true failure-free rate is 50% and the device is assumed to be safe (true PAE rate is 1%). The table shows the largest Type I error rate for the trial in the simulations was 0.023, still below the 2.5% threshold.

In adaptive trials, the enrollment rate to the trial directly impacts the amount of information that is available at the time of the interim and may influence the probability of stopping at the interim. In this simulation, however, there is little to no impact of different enrollment rates on Type I error, and notably, all values are below 2.5%.

Table 4: *Type I error rate*

		Pr(Declaring Success)		
Failure-free Rate	PAE Rate	Expected	Fast	Slow
0.50	0.01	0.011	0.007	0.010
0.50	0.07	0.008	0.009	0.007
0.50	0.08	0.007	0.007	0.006
0.50	0.10	0.004	0.005	0.004
0.50	0.12	0.001	0.001	0.001
0.50	0.14	0.000	0.000	0.000
0.55	0.14	0.003	0.004	0.003
0.60	0.14	0.012	0.013	0.012
0.65	0.14	0.019	0.021	0.019
0.70	0.14	0.021	0.021	0.020
0.99	0.14	0.023	0.021	0.023

30.4.2 Probability of Success

For the full range of effectiveness and safety scenarios, this section summarizes the probability of trial success for the expected enrollment rate. Table 5 summarizes the probability of success in the following ways:

- **Both**: the proportion of virtual trials that were successful (on both endpoints) either at an interim or at the final analysis
- **Effectiveness**: the proportion of trials that were successful on the effectiveness endpoint
- **Safety**: the proportion of trials that were successful on the safety endpoint

- **Early**: the proportion of trials that met the criteria for success (on both endpoints) at the interim analysis
- **Final**: the proportion of trials that met the criteria for success (on both endpoints) at the final analysis when the early success is not declared.

If the true PAE rate is 7% and the true failure-free rate is 65%, the trial has approximately 81.7% power. Under this scenario, 64.8% of the simulated trials claimed success at the interim and an additional 16.9% of trials achieved success at the final analysis.

Table 5: *Pr(Declaring Success) (Expected Enrollment)*

Failure-free Rate	PAE Rate	Pr(Declaring Success) Both	Effectiveness	Safety	Early	Final
0.50	0.07	0.008	0.010	0.856	0.002	0.007
	0.08	0.007	0.010	0.696	0.001	0.006
	0.1	0.004	0.009	0.342	0.001	0.003
	0.12	0.001	0.010	0.105	0.000	0.001
	0.14	0.000	0.009	0.021	0.000	0.000
0.55	0.07	0.144	0.169	0.853	0.046	0.098
	0.08	0.114	0.161	0.710	0.035	0.079
	0.1	0.058	0.160	0.352	0.018	0.040
	0.12	0.016	0.148	0.101	0.006	0.010
	0.14	0.003	0.153	0.020	0.001	0.002
0.60	0.07	0.530	0.625	0.847	0.270	0.261
	0.08	0.439	0.613	0.705	0.225	0.214
	0.1	0.209	0.613	0.340	0.104	0.105
	0.12	0.063	0.625	0.104	0.030	0.033
	0.14	0.012	0.617	0.021	0.006	0.006
0.65	0.07	0.817	0.952	0.860	0.648	0.169
	0.08	0.661	0.953	0.696	0.522	0.138
	0.1	0.325	0.951	0.338	0.260	0.064
	0.12	0.099	0.954	0.104	0.078	0.021
	0.14	0.019	0.948	0.021	0.015	0.004
0.70	0.07	0.852	0.999	0.853	0.824	0.028
	0.08	0.699	0.999	0.700	0.680	0.019
	0.1	0.347	0.998	0.347	0.336	0.011
	0.12	0.107	0.999	0.107	0.104	0.003
	0.14	0.021	0.999	0.021	0.020	0.001

30.4.3 Sensitivity to Enrollment Rate

In this section, we repeat the operating characteristics of the previous section under different trial enrollment rates. Table 6 and Table 7 show the probability of success for the 5 different categories under the fast and slow enrollment rates respectively.

In this simulation, there is little to no impact from different enrollment rates on overall power, and notably, all values are about 81.7% when the true PAE rate is 7% and the true failure-free rate is 65%. However, it seems there is some impact on the early success rate for different enrollment rates since the amount of information available at the time of the interim is changed according to the enrollment rate. If the enrollment is slower than expected, the trial has a little higher ability to reach a success decision before the final analysis. With the fast enrollment, the trial has a lower ability to reach early success.

Table 6: *Pr(Declaring Success) (Fast Enrollment)*

Failure-free Rate	PAE Rate	Pr(Declaring Success) Both	Effectiveness	Safety	Early	Final
0.50	0.07	0.009	0.010	0.855	0.002	0.007
	0.08	0.007	0.010	0.706	0.001	0.006
	0.1	0.005	0.010	0.342	0.001	0.004
	0.12	0.001	0.010	0.100	0.000	0.001
	0.14	0.000	0.009	0.023	0.000	0.000
0.55	0.07	0.132	0.155	0.861	0.040	0.092
	0.08	0.107	0.151	0.705	0.030	0.077
	0.1	0.054	0.154	0.345	0.016	0.039
	0.12	0.015	0.144	0.102	0.005	0.009
	0.14	0.004	0.153	0.021	0.001	0.003
0.60	0.07	0.539	0.620	0.866	0.237	0.302
	0.08	0.453	0.631	0.712	0.208	0.245
	0.1	0.216	0.629	0.336	0.095	0.121
	0.12	0.063	0.616	0.100	0.026	0.037
	0.14	0.013	0.618	0.022	0.006	0.008
0.65	0.07	0.818	0.951	0.859	0.621	0.196
	0.08	0.669	0.957	0.700	0.503	0.166
	0.1	0.316	0.952	0.330	0.239	0.076
	0.12	0.097	0.953	0.101	0.073	0.024
	0.14	0.021	0.954	0.022	0.016	0.006
0.70	0.07	0.847	0.999	0.848	0.817	0.030

0.08	0.683	0.999	0.684	0.658	0.025
0.1	0.347	0.999	0.348	0.334	0.014
0.12	0.102	0.999	0.102	0.099	0.003
0.14	0.021	0.999	0.021	0.021	0.000

Table 7: Pr(Declaring Success) (Slow Enrollment)

Failure-free Rate	PAE Rate	Pr(Declaring Success) Both	Effectiveness	Safety	Early	Final
0.50	0.07	0.007	0.009	0.862	0.002	0.006
	0.08	0.006	0.008	0.708	0.002	0.004
	0.1	0.004	0.010	0.334	0.002	0.002
	0.12	0.001	0.008	0.101	0.000	0.001
	0.14	0.000	0.008	0.022	0.000	0.000
0.55	0.07	0.136	0.155	0.868	0.051	0.085
	0.08	0.111	0.158	0.694	0.038	0.072
	0.1	0.053	0.155	0.335	0.015	0.038
	0.12	0.015	0.146	0.102	0.005	0.010
	0.14	0.003	0.146	0.023	0.001	0.003
0.60	0.07	0.546	0.632	0.857	0.299	0.247
	0.08	0.434	0.623	0.691	0.238	0.195
	0.1	0.206	0.612	0.337	0.113	0.093
	0.12	0.064	0.610	0.099	0.035	0.029
	0.14	0.012	0.609	0.020	0.007	0.006
0.65	0.07	0.816	0.955	0.855	0.670	0.146
	0.08	0.676	0.961	0.705	0.560	0.116
	0.1	0.327	0.954	0.342	0.262	0.065
	0.12	0.101	0.952	0.104	0.083	0.018
	0.14	0.019	0.948	0.020	0.015	0.004
0.70	0.07	0.850	1.000	0.850	0.834	0.016
	0.08	0.700	0.999	0.700	0.685	0.015
	0.1	0.324	0.999	0.324	0.318	0.007
	0.12	0.097	0.999	0.097	0.095	0.002
	0.14	0.020	0.999	0.020	0.020	0.000