QDOT – FAST

Clinical Study for Safety and Acute Performance Evaluation of the THERMOCOOL SMARTTOUCH® SF-5D System used with Fast Ablation Mode in Treatment of Patients with Paroxysmal Atrial Fibrillation.

Protocol Number:	BWI_2017_02
Sponsor:	Biosense Webster, Inc., a division of Johnson & Johnson with registered office at 33 Technology Drive, Irvine, CA 92618
Operating Company:	Johnson & Johnson Medical NV/SA with registered office at Leonardo Da Vincilaan 15, 1831 Diegem, Belgium, represented by Nathalie Macours.
Funded by:	Biosense Webster, Inc., part of the Johnson & Johnson family of companies.
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History of Changes:

Version – Date	Description
V1.0 – 21 DEC 2017	Original document

The THERMOCOOL SMARTTOUCH® SF-5D catheter and system is for investigational device use only and is not commercially available anywhere in the world. QDOT MICRO™ catheter (THERMOCOOL SMARTTOUCH® SF-5D catheter) is an internal Biosense Webster name and other than as used in the present clinical investigation, is not intended for any other external use. The final commercial or trade name of the THERMOCOOL SMARTTOUCH® SF-5D catheter and system may be different.

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List of Acronyms and Abbreviations

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

Acronym/ Abbreviation	Expanded Term
LVEF	Left Ventricular Ejection Fraction
MEDDEV	Medical Device Directive
MI	Myocardial Infarction
MoCA	Montreal Cognitive Assessment
MOH	Ministry of Health
MRI	Magnetic Resonance Imaging
mRS	Modified Ranking Scale
NIHSS	National Institute of Health Stroke Scale
NOS	Not Other Specified
NSR	Normal Sinus Rhythm
NYHA	New York Heart Association
PAE	Primary Adverse Event
PAF	Paroxysmal Atrial Fibrillation
PE	Primary Endpoint
PI	Principal Investigator
PIU	Patient Interface Unit
PN	Phrenic Nerve
PNP	Phrenic Nerve Paralysis
PP	Per Protocol
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QA	Quality Assurance
QoL	Quality of Life
RA	Right Atria
RBA	Risk-Benefit Analysis
RF	Radiofrequency
RV	Right Ventricle
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SP	Safety Population
SDV	Source Data Verification
SVC	Superior Vena Cava
SW	Software
TEE	Transesophageal Echocardiography
TGA	Temperature Guided Ablation /Fast Ablation
TIA	Transient Ischemic Attack
TS	Transseptal
TTE	Transthoracic Echocardiography
UADE	Unanticipated Adverse Device Effect
UNS	Unscheduled
US	United States
USADE	Unanticipated Serious Adverse Device Effect

Key roles and Responsible Parties

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Whereas, the Clinical Study is sponsored by Biosense Webster Inc., Johnson and Johnson Medical NV/SA with registered offices at Leonardo Da Vincilaan 15, 1831 Diegem, Belgium, has been duly appointed by the Sponsor to conduct the Clinical Study on its behalf.

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

Protocol Summary

Full Title	Clinical study for safety and acute performance evaluation of the THERMOCOOL SMARTTOUCH® SF-5D system used with Fast Ablation mode in treatment of patients with Paroxysmal Atrial Fibrillation.
Protocol Number	BWI_2017_02
Short Title	QDOT-FAST
Sponsor	Biosense Webster, Inc. 33 Technology Drive Irvine, CA 92618 USA Tel +1 800 729 9010
Indication	Paroxysmal Atrial Fibrillation
Study Article Description	THERMOCOOL SMARTTOUCH® SF-5D Catheter [redacted], also named QDOT MICRO™, a novel radiofrequency ablation catheter combining microelectrodes, thermocouples, porous tip irrigation and contact force sensing nMARQ™ Multi-Channel RF Generator [redacted] with Software V[redacted] including TGA mode. The TGA mode (Temperature Guided Ablation) is designed to deliver high power [redacted] in a very short ablation session [redacted] under temperature control.
Study Design	The purpose of this study is to evaluate safety and acute performance of the THERMOCOOL SMARTTOUCH® SF-5D catheter used in combination with the nMARQ™ Multi-Channel RF Generator with TGA mode in the treatment of Paroxysmal Atrial Fibrillation (PAF) during standard electrophysiology mapping and RF ablation procedures. The QDOT-FAST study is a prospective, multi-center, non-randomized, interventional clinical study.
Sample Size	50 subjects will be enrolled. Because this study is a feasibility study, there is no statistical power calculation and no hypothesis to be tested. Fifty subjects are deemed sufficient to clinically characterize safety and acute outcomes.
Study Population	Paroxysmal AF subjects who are scheduled to undergo a clinically-indicated ablation procedure for management of their paroxysmal AF will be the target population for screening.
Geographic areas to be included	Up to 10 centers in Europe
Study Duration	Approximately 12 months
Participant Duration	Subjects will be followed till 3-months post-procedure
Procedure Description	Subjects will arrive to the electrophysiology laboratory for their ablation procedure and will undergo preparation for the procedure per the hospital's standard protocol (discretion of investigator). The AF Ablation procedure will follow below sequence: • Anatomical mapping of the left atrium • Introduction of the study catheter • Circumferential Pulmonary Vein Isolation (PVI) using TGA mode

<table>
<tr><td></td><td>

Confirmation of PVI with Lasso® or Pentaray® (or other at investigators discretion)
Confirmation of entrance block with adenosine/isoproterenol challenge

In this study protocol, TGA mode is to be used as the primary mode for pulmonary vein isolation. Only after the investigator deems TGA mode unable to achieve PVI should the study catheter in Q-mode be used to complete the procedure.
</td></tr>
<tr><td>Primary Endpoint</td><td>
Acute Safety:
The primary safety endpoint is the incidence of Primary Adverse Events (PAEs) (within seven (7) days of the initial mapping and ablation procedure). PAEs include the following AEs:
<table>
<tr><td>Atrio-Esophageal Fistula*</td><td>Phrenic Nerve Paralysis</td></tr>
<tr><td>Cardiac Tamponade/perforation</td><td>Pulmonary Vein Stenosis*</td></tr>
<tr><td>Death*</td><td>Stroke/CVA</td></tr>
<tr><td>Major Vascular Access Complication/Bleeding</td><td>Thromboembolism</td></tr>
<tr><td>Myocardial Infarction</td><td>TIA</td></tr>
</table>
* Device or procedure related death, pulmonary vein stenosis and atrio-esophageal fistula that occur greater than one week (7 days) post-procedure are considered and analyzed as primary AEs.

Acute Effectiveness:
Acute Procedural Success defined as confirmation of entrance block in all targeted PVs after adenosine and/or isoproterenol challenge.

The use of a non-study catheter for PVI will be considered an effectiveness failure.
</td></tr>
<tr><td>Secondary Endpoints</td><td>
Safety
- Incidence of Serious Adverse Device Effects (SADEs)
- Incidence of Serious Adverse Events (SAEs) within 7 days (early-onset), >7-30 days (peri-procedural) and >30 days (late onset) of initial ablation procedure
- Incidence of non-serious adverse events
- Incidence of pre-and post-ablation asymptomatic and symptomatic cerebral emboli as determined by MRI evaluations
- Incidence of new or worsening neurological deficits compared to baseline
- Summary of NIHSS, mRS and MoCA scores at baseline and follow-up timepoints

Effectiveness
- PVI achieved with TGA mode only among all targeted veins and by subject
- PVI achieved with combined use of TGA and Q-mode among all targeted veins and by subject
- Ablation of acute reconnection (touch-up) among all targeted veins and by subject
- Ablation by a non-study catheter among all targeted veins and by subject
- Touch-up applications with TGA, Q-mode and non-study catheter applications

Additional analyses on procedural data, including but not limited to:
- Use of QDOT Micro™ catheter ablation outside the PV area
- Use of a non-study catheter for ablation outside the PV area
- Total procedure time, mapping time, PV ablation time, total ablation time, RF application time, LA dwell time
- Total number of RF applications, % TGA applications and % Q-mode applications
- Anatomical location of touch-up applications
- Temperature, power, contact force, impedance
</td></tr>
</table>

	- Total Fluoroscopy time/dose
Inclusion Criteria	Subjects must meet ALL the following inclusion criteria to be eligible for participation in this clinical investigation: 1. Age 18 or older. 2. Signed the Patient Informed Consent Form (ICF). 3. Diagnosed with symptomatic PAF 4. Selected for catheter ablation through pulmonary vein isolation. 5. Able and willing to comply with all pre-, post-, and follow-up testing and requirements (e.g. patient not confined by a court ruling).
Exclusion Criteria	Subjects who meet ANY of the following exclusion criteria are not eligible for enrollment: 1. Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause. 2. Previous surgical or catheter ablation for atrial fibrillation. 3. Previously diagnosed with persistent, longstanding AF and/or continuous AF >7 days, or >48 hrs. terminated by cardioversion. 4. Documented Left Atrial thrombus on baseline/pre-procedure imaging. 5. Any carotid stenting or endarterectomy. 6. Left atrial (LA) size >50mm. 7. Left Ventricular ejection fraction (LVEF) <40%. 8. Uncontrolled heart failure or New York Heart Association (NYHA) function class III or IV. 9. History of blood clotting or bleeding abnormalities 10. Contraindication to anticoagulation 11. History of a documented thromboembolic event (including transient ischemic attack (TIA)) within the past 12 months. 12. Previous percutaneous coronary intervention (PCI) or myocardial Infarction (MI) within the past 2 months. 13. Coronary artery bypass grafting (CABG) in conjunction with valvular surgery, cardiac surgery (e.g. ventriculotomy, atriotomy) or valvular cardiac (surgical or percutaneous) procedure. 14. Rheumatic Heart Disease 15. Awaiting cardiac transplantation or other cardiac surgery within the next 12 months. 16. Unstable angina. 17. 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. 18. Acute illness, active systemic infection, or sepsis. 19. Presence of atrial myxoma, interatrial baffle or patch 20. Presence of intramural thrombus, tumor or other abnormality that precludes catheter introduction or manipulation. 21. Presence of a condition that precludes vascular access. 22. Presence of implanted pacemaker or implantable cardioverter-defibrillator (ICD). 23. Presence of IVC filter 24. Significant congenital anomaly or a medical problem that in the opinion of the investigator would preclude enrollment in this trial. 25. Currently enrolled in an investigational study evaluating another device, biologic, or drug. 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 clinical investigation. 27. Life expectancy or other disease processes likely to limit survival to less than 12 months. 28. Presenting contra-indication for the devices used in the study, as indicated in the respective instructions for use. 29. Categorized as vulnerable population and requires special treatment with respect to safeguards of well-being 30. Contraindication to use of contrast agents for MRI such as advanced renal disease, etc. (at PI discretion) 31. Presence of iron-containing metal fragments in the body 32. Unresolved pre-existing neurological deficit.
Statistical Analysis	All data will be summarized by descriptive analyses. No formal statistical inference will be made. Sub-analyses will be done for subjects where TGA was the only application mode used and for subjects where applications were done through a mixture of TGA and Q-mode.
Interim Analysis	Analysis of acute outcomes may be done prior to completion of the study FU period and after completion of all study procedures.
Safety Monitoring	Safety review will be performed by the medical safety officer as described by Safety Management Plan.
Time and Events Schedule	See table 1 below

Table 1 Summary of Subject Assessments

Assessments	Pre-ablation	Pre-discharge	7D (D6-8)	M1 (D23-37)	M3 (D76-104)	UNS
Clinic visit	●			● [9/10]	●	●
Phone Call			● [1]			
Patient Informed Consent[2]/Demographics	●					
Medical/AF history	●					
Cardiac Medication and anti-coagulation Regimen	●	●	●	● [9]	●	●
CHA2DS2-Vasc Score	●					
NYHA functional Class Scale	●				●	
Pregnancy Test	● [3]					
Transthoracic Echo (TTE)	● [4]	●				
LA thrombus detection	● [5]					
ECG	● [5]	● [6]			● [6]	● [6]
Adverse events	●	●	●		●	●
AFL/AT/AF occurrence and repeat ablation		●	●		●	●
Endoscopy		● [8]				
Cerebral MRI	● [7]	● [8]		● [9]	● [9]	● [10]
Neurological Exam	● [7]	● [8]		● [9]	● [9]	● [10]
NIH Stroke Scale	● [7]	● [8]		● [9]	● [9]	● [10]
mRS	● [7]			● [9]	● [9]	● [10]
MoCA	● [7]			● [9]	● [9]	● [10]

1. May be substituted with a clinic visit.
2. To be completed within 60 days prior to ablation procedure
3. In all women of childbearing age and potential. To be completed within 1 week prior to ablation procedure.
4. To be performed within 30 days prior to procedure to determine the LA size and LVEF%, 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.
5. To be completed the day before or the day of the study ablation procedure. Imaging modality TEE, ICE, CT or MRI.
6. To be collected if completed as standard of care.
7. To be completed within 72-hours pre-procedure.
8. To be completed within 72-hours post-procedure.
9. To be undertaken/collected if neurologic symptoms and/or new cerebral ischemic lesions identified/CVA/TIA reported in a prior evaluation.
10. To be completed only if a previous mandated test was missed, or if subject reports neurologic difficulties between scheduled follow-up visits and unscheduled assessment per investigator approval

1. Background Information and Scientific Rationale

1.1. Background Information

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

Radiofrequency (RF) catheter ablation has provided excellent results for treating many types of supraventricular arrhythmias.[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.

1.2. Rationale for Design of the clinical investigation

The Biosense Webster THERMOCOOL SMARTTOUCH® SF-5D 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[redacted]

[redacted]

1.2.1. *Previous Experience with the THERMOCOOL® SMARTTOUCH® SF catheter*

The THERMOCOOL® SMARTTOUCH® SF catheter, approved in the European Union, features a porous electrode tip (56 small holes) in contrast to the predecessor THERMOCOOL®SMARTTOUCH® device, which featured 6 larger holes at the distal electrode tip. In subjects with paroxysmal AF, the THERMOCOOL® SMARTTOUCH® SF catheter with Surround Flow (SF) technology was as successful as the predecessor catheter in achieving PV isolation, with delivery of similar amounts of RF energy.

Moreover, the saline volume administered by the catheter was reduced when compared to the SMARTTOUCH® Catheter.[31] Procedural efficiency was also enhanced; time to PV isolation and total RF duration,[32,33] as well as saline irrigation volume,[33,34] were diminished in paroxysmal AF subjects who underwent ablation with the SMARTTOUCH® SF catheter compared to the THERMOCOOL® SMARTTOUCH® catheter without SF technology.

1.2.2. *Previous Experience with THERMOCOOL SMARTTOUCH® SF-5D catheter*

This clinical feasibility study will be the first experience using THERMOCOOL SMARTTOUCH SF-5D[redacted] in conjunction with the nMARQ™ Multi-Channel RF Generator ([redacted], including TGA mode.

Bench and animal testing has been performed using the THERMOCOOL SMARTTOUCH SF-5D Catheter and the nMARQ™ Multi-channel RF Generator. Please refer to the Investigator Brochure for detailed summaries of the test protocols and corresponding reports. A synopsis of the In Vivo animal studies is presented below.

1.3. [redacted]

[redacted]

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1.4. Potential Risk and Benefit

RF catheter ablation has been used for over 20 years, and the risks and complications are well understood. A summary of risks associated with catheter ablation, including analysis of and plans to minimize these risks is provided below:

1.4.1. *Known Potential Risks*

Known Potential Risks associated with catheter RF ablation procedure

The risk of **pulmonary adverse events** (e.g., PV stenosis, thrombus and cardiac perforation) associated with an AF ablation procedure targeting the pulmonary veins is considered small (<4%).[16-22]

Arterial or venous injury, including arterial dissection, thrombosis, occlusion or hemorrhage at the **catheter insertion sites** or at other sites along the vessels can occur (risk <1%).[23,24] These types of injuries may cause hemorrhage, hematoma or ischemic injury to an extremity or major organ.

RF current may cause **occlusion of a coronary artery**, either by direct thermal damage, spasm, or thrombosis. Experience at numerous clinical sites/centers suggests that the risk of coronary occlusion is less than 0.5%.[23,24] Coronary arterial occlusion could produce myocardial infarction (MI), angina or death.

The application of RF 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.

A thrombus may form on the ablation electrode during the application of RF current, usually indicated by an impedance rise; however, this can also occur in the absence of an impedance rise. The thrombus could become dislodged and embolize to produce a stroke, myocardial infarction (MI), or other ischemic injury. The possible embolic sources include thrombus formation on the ablation catheter tip and sheath, debris from steam pop and charring, preexisting thrombus in the heart and air embolus. The risk of an embolus is reduced by quickly terminating the application of

current after an impedance rise, which limits the size of the coagulum on the electrode. Probably the most important aspect of the THERMOCOOL® family of catheters is the absence or very low likelihood of thrombus formation during RF.

Thrombus formation on the endocardium following ablation may produce an arterial or pulmonary embolus. This risk may be reduced using aspirin or other anticoagulant therapy, at the discretion of the investigator.

Cardiac perforation may result from catheter manipulation or application of RF current. Published risks of cardiac perforation range from <1% to 2.5%.[25,8,26-29] This may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. In a recent study using the THERMOCOOL SMARTTOUCH® Catheter with contact force sensing technology, there were 4 (2.48%, 4/161) reported incidents of tamponade.[8,26] Additionally, in the SMART-SF study using a new investigational catheter with contact force sensing technology the observed incidence of tamponade was 1.3% (2/159). Significant hemodynamic compromise can result in neurologic injury or death. An increased risk of cardiac perforation during ablation may be associated with the use of saline-irrigated electrode catheter due to its ability to create a larger, deeper lesion.

Using the standard RF power settings, i.e. between 25 to 45 watts, at current application duration, such as at 30 s, it could deliver up to 1200 J to atrial tissue and provide the potential risk of overheating.[14] The risk of cardiac perforation is even higher in thin walled, smooth muscle tissue and veins with the conventional approach, when each ablation stays longer on the same spot. In current clinical practice, RF application duration parameter becomes a crucial biophysical timer to monitor the safety threshold. In this protocol, the novel high power and short duration algorithm reduces the application duration significantly. It has the potential to deliver less energy and to generate uniform lesions without collateral damages, in particular in a thin walled atrial chamber.

Peri-esophageal vagal nerve injury or pyloric spasm after left atrial catheter ablation of AF can occur when RF energy is applied to the posterior wall of the LA.[4] While these complications are rare (approximately < 1%), they can potentially compromise the clinical outcome severely, requiring surgical treatment.[30,31] While there is no established method to prevent injury to the vagal nerves, the risk may be reduced by using the same techniques used to avoid an AEF (atrial esophageal fistula). [4]

Injury to a cardiac valve may result from catheter manipulation or the application of RF current (risk <1%).[23,24] This may produce valvular insufficiency and possibly require surgical valve replacement.

The application of RF energy along the posterior left atrium can result in thermal injury to the esophagus and the formation of an **atrio-esophageal fistula**. This is a rare (0.04%) but severe complication of RF ablation requiring surgical intervention or that may result in permanent impairment.[25,28] Reducing power at sites in close proximity to and/or avoiding sites directly over the esophagus may reduce the risk of thermal injury.

Injury to the phrenic nerve may occur as a result of RF application in the region of right pulmonary veins. The reported incidence of phrenic nerve injury varies from 0% to 0.48% when RF energy is used for catheter ablation.[32,33] Prior to ablation in the region of the right superior pulmonary vein, precautionary measures are recommended to be performed by investigators to evaluate proximity to the phrenic nerve, such as pacing maneuvers.

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%).[34-36]

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%).[37-41]
Hemorrhage could occur as a result of anticoagulation (risk <0.5%), which may require transfusion.[23,24]

The percutaneous procedure carries **risk of infection**, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%).[23,24] This risk can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents.

Investigational device related risks

THERMOCOOL SMARTTOUCH® SF-5D catheter and nMARQ Multi-Channel RF generator with TGA mode

Although the risks are low, anticipated risks /major complications associated with the catheter ablation procedure in general could still occur during the procedure. During the TGA design phase (ref RBA section 6.1.1), systematic proactive risk analyses concluded that no new hazards and harms associated with TGA (FAST mode) have been identified to cause any foreseeable risks. At this juncture, no new complications are anticipated concerning the TGA ablations.

The nMARQ™ Multi-Channel RF Generator (D-1341-07) (SW version 2.3.1) was CE marked on Oct 25, 2013. In order to allow for an interface with the THERMOCOOL SMARTTOUCH® SF-5D Catheter, the software was modified to SW version 3.0.1. As a result of the software modification, the nMARQ™ Multi-Channel RF Generator will be designated as an investigational device. Further reference can be made to the User manual and addendum, for more information. Enhanced versions of the SW v3.0.1 might be released and used during the course of this study. A protocol Amendment will be submitted for approval if any additional significant risks would be identified in newly released software versions.

The software with TGA mode using the investigational catheter has been validated in both bench top and animal testing at the system level. The design of the software has been independently validated to perform against functional requirements. Accuracy of the generator as it relates to: temperature and power was identified to be the highest risk related to the device. Therefore, 100% testing of generator power, temperature and impedance is included in the lot release protocol, prior to the release to the study.

Robust testing of the devices from the component and the system level, within simulated clinical conditions, including certain up limits & extreme clinical scenarios, was determined to be successful with no adverse events identified.

For SW V3.0.1 there are no anticipated potential direct risks to the subject, the risk is mitigated by the temp cutoff setting of the generator and the optimization of the target temperature. Further reference can be made to the pre-clinical testing reports and Investigator Brochure for more information.

1.4.2. *Minimization of Risk*

The criteria for subject selection, methods, personnel, facilities, and training that have been specified in this study are intended to minimize the risk to subjects undergoing this procedure.

Patient selection: 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 exclude subjects with a medical history or condition that increases their risk of adverse events (refer to Section 4.2 for the Exclusion Criteria).

Pre-procedure imaging: All subjects will have pre-procedure imaging as described in section 8.2 to screen for the presence of LA thrombus, which is intended to decrease the potential for thromboembolic complications.

Within procedure safeguard: Investigators will undergo training on the use of the THERMOCOOL SMARTTOUCH® SF-5D technology prior to subject enrollment. Investigators skilled in intracardiac mapping and ablation of AF with the use of RF ablation catheters containing contact force technology will be selected for participation in the study. All investigators are required to receive the training prior the enrollment. AF ablation procedures will be performed in electrophysiology laboratories with the assistance of skilled nurses and technicians. The detailed workflow for the procedure is provided in the protocol, including the target temperature, the cut-off temperature, the range of the contact force, the stability using Visitag, Respiratory compensation and Automatic tags. To proactively manage the four big "watch-out" complications (Atrio-Esophageal Fistula, PV stenosis, Phrenic nerve paralysis and cerebral embolism) for a RF ablation procedure, the protocol proposes the following:

- In order to prevent esophageal injury, intraluminal esophageal monitoring is required for the study
- The risk of cerebral lesions will be monitored by pre-post cerebral MRI examination monitoring for cerebral embolism.
- The risk of PV stenosis will be minimized by monitoring that RF energy applications are at least 1 to 2 cm outside the PV ostium to isolate the left and right-sided PVs; Subjects presenting suggestive symptoms for PV stenosis, should undergo the cardiac CT/MRI;
- The risk of PNP will be minimized by monitoring the PN with pacing maneuvers before the ablation. High output pacing is recommended at vulnerable sites and avoid ablations at the area that stimulate the PN

Post-procedural management: In accordance with the 2017 HRS expert consensus statement[4], all subjects will be recommended to be maintained on systemic oral anticoagulation therapy for at least two months post-procedure, beginning within 6 hours post-procedure. After two-months post-procedure, a decision regarding continuation of systemic anti-coagulation agents will be based on the patient risk for thromboembolism. Systemic oral anticoagulation will be recommended to be continued beyond two-months post-ablation in patients with CHA_2DS_2-VASc score ≥2.

Safety data during enrollment and follow-up will be closely monitored and evaluated per the specific safety management plan for the study. Also, refer to safety section 9 for more information on safety management.

1.4.3. *Known Potential Benefits*

The Biosense Webster THERMOCOOL SMARTTOUCH® SF-5D Catheter is a steerable multi-electrode luminal catheter with a deflectable tip designed to facilitate electrophysiological mapping of the heart and to transmit radiofrequency (RF) current to the catheter tip electrode for ablation purposes. In addition to force-sensing technology, the catheter incorporates six thermocouple temperature sensors and three micro electrodes embedded in the 3.5 mm tip electrode.

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

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

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

With improved contact force information and temperature feedback in any tip tissue orientation, the new THERMOCOOL SMARTTOUCH® SF-5D catheter is designed to create durable lesions, in shorter time, with fewer ablation applications, and improved irrigation flow decreasing the opportunity for char and coagulum formation.

The expected benefits of the THERMOCOOL SMARTTOUCH® SF-5D Ablation System: nMARQ™ Multi-Channel RF Generator (D-1341-07, SW version 3.0.1) and THERMOCOOL SMARTTOUCH® SF-5D catheter may improve safety and efficiency. The System may potentially:

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

Further reference can be made to the Risk-Benefit Analysis (RBA) for more information.

2. Objectives

The primary objective of this clinical investigation is to assess the safety and acute performance of the THERMOCOOL SMARTTOUCH® SF-5D system used with the TGA algorithm, in the isolation of the atrial pulmonary veins in treatment of patients diagnosed with Paroxysmal Atrial Fibrillation (PAF). Specifically, to demonstrate:

- Safety based on the incidence of early onset Primary Adverse Events (PAEs) (within seven (7) days of the initial ablation procedure).
- Acute system performance based on acute procedural success defined as confirmation of entrance block in all targeted PVs after adenosine and/or isoproterenol challenge.

Secondary objectives of the study relate to further evaluation of safety with regards to (serious) adverse events and neurological incidents up to 3 months following procedure. Secondary evaluation of effectiveness and workflow will be done through characterization of the TGA and Q-mode use for PVI, assessment of acute reconnection during the procedure and through description of procedural parameters.

3. Study Design and Endpoints

3.1. Description of the Study Design

The QDOT-FAST study is a prospective, multi-center, non-randomized clinical study to evaluate the safety and acute performance of the THERMOCOOL SMARTTOUCH® SF-5D system with the TGA algorithm in patients diagnosed with Paroxysmal Atrial Fibrillation (PAF).

The study population will consist of up to 50 subjects with PAF as an indication for radiofrequency (RF) ablation. PAF is defined as AF that terminates spontaneously or with intervention within 7 days of onset. Episodes may recur with variable frequency (HRS ACC guidelines, 2017).[4]

The study will be conducted at up to 10 sites in Europe. Follow-up will be conducted at 7 days, 1 month and 3-month post-ablation procedure.

3.2. Study Endpoints

3.2.1. *Primary Endpoint(s)*

Acute Safety

The primary safety endpoint is the incidence of Primary Adverse Events (PAEs) (within seven (7) days of the initial mapping and ablation procedure). Primary Adverse Events are one of the following adverse events listed below. (refer to section 9.1.3 for a complete list and description/criteria).

Atrio-Esophageal Fistula (AEF)*	Phrenic Nerve Paralysis (PNP)
Cardiac Tamponade/perforation	Pulmonary Vein Stenosis*
Death*	Stroke/CVA
Major Vascular Access Complication/Bleeding	Thromboembolism
Myocardial Infarction	TIA

* Device or procedure related death, pulmonary vein stenosis and atrio-esophageal fistula, that occur greater than one week (7 days) post-procedure are considered and analyzed as primary AEs.

Acute Effectiveness

Acute procedural success defined as confirmation of entrance block in all targeted PVs after adenosine and/or isoproterenol challenge.

3.2.2. *Secondary Endpoint(s)*

Safety

- Incidence of Serious Adverse Device Effects (SADEs)
- Incidence of Serious Adverse Events (SAEs) within 7 days (early-onset), >7-30 days (peri-procedural) and >30 days (late onset) of initial ablation procedure
- Incidence of non-serious adverse events
- Incidence of pre-and post-ablation asymptomatic and symptomatic cerebral emboli as determined by MRI evaluations
- Incidence of new or worsening neurological deficits compared to baseline
- Summary of NIHSS, mRS and MoCA scores at baseline and follow-up timepoints

Effectiveness

- PVI achieved with TGA mode only among all targeted veins and by subject
- PVI achieved with combined use of TGA and Q-mode among all targeted veins and by subject
- Ablation of acute reconnection (touch-up) among all targeted veins and by subject
- Touch-up applications with TGA, Q-mode and non-study catheter applications
- PV ablation by a non-study catheter among all targeted veins and by subject

Additional analyses on procedural data, including but not limited to:

- Use of QDOT Micro™ catheter ablation outside the PV area
- Use of a non-study catheter for ablation outside the PV area
- Total procedure time, mapping time, PV ablation time, total ablation time, RF application time, LA dwell time
- Total number of RF applications, % TGA applications and % Q-mode applications
- Anatomical location of touch-up applications
- Temperature, power, contact force, impedance
- Total Fluoroscopy time/dose

4. Study Population

4.1. Participant Inclusion Criteria

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

1. Age 18 or older.
2. Signed the Patient Informed Consent Form (ICF).
3. Diagnosed with symptomatic PAF
4. Selected for catheter ablation through pulmonary vein isolation.
5. Able and willing to comply with all pre-, post-, and follow-up testing and requirements (I.e. patient not confined by a court ruling).

4.2. Participant Exclusion Criteria

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

1. Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause.
2. Previous surgical or catheter ablation for atrial fibrillation.
3. Previously diagnosed with persistent, longstanding AF and/or continuous AF >7 days, or >48 hrs. terminated by cardioversion.
4. Documented Left Atrial thrombus on baseline/pre-procedure imaging.
5. Any carotid stenting or endarterectomy.
6. Left atrial (LA) size >50mm.
7. Left Ventricular ejection fraction (LVEF) <40%.
8. Uncontrolled heart failure or New York Heart Association (NYHA) function class III or IV.
9. History of blood clotting or bleeding abnormalities
10. Contraindication to anticoagulation
11. History of a documented thromboembolic event (including transient ischemic attack (TIA)) within the past 12 months.
12. Previous percutaneous coronary intervention (PCI) or myocardial Infarction (MI) within the past 2 months.
13. Coronary artery bypass grafting (CABG) in conjunction with valvular surgery, cardiac surgery (e.g. ventriculotomy, atriotomy) or valvular cardiac (surgical or percutaneous) procedure.
14. Rheumatic Heart Disease
15. Awaiting cardiac transplantation or other cardiac surgery within the next 12 months.
16. Unstable angina.
17. 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.
18. Acute illness, active systemic infection, or sepsis.
19. Presence of atrial myxoma, interatrial baffle or patch
20. Presence of intramural thrombus, tumor or other abnormality that precludes catheter introduction or manipulation.
21. Presence of a condition that precludes vascular access.
22. Presence of implanted pacemaker or implantable cardioverter-defibrillator (ICD).
23. Presence of IVC filter
24. Significant congenital anomaly or a medical problem that in the opinion of the investigator would preclude enrollment in this trial.
25. Currently enrolled in an investigational study evaluating another device, biologic, or drug.
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 clinical investigation.
27. Life expectancy or other disease processes likely to limit survival to less than 12 months.
28. Presenting contra-indication for the devices used in the study, as indicated in the respective instructions for use.
29. Categorized as vulnerable population and requires special treatment with respect to safeguards of well-being
30. Contraindication to use of contrast agents for MRI such as advanced renal disease, etc. (at PI discretion)
31. Presence of iron-containing metal fragments in the body
32. Unresolved pre-existing neurological deficit.

4.3. Participant Withdrawal or Termination

4.3.1. *Reasons for Withdrawal or Termination*

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

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

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

Every subject should be encouraged to remain in the study until they have completed the protocol required 3-months follow-up period.

4.3.2. *Handling of Participant Withdrawals or Termination*

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

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

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

4.4. Subject Enrollment Disposition

The following subject groups are defined:

- **Enrolled Subjects:** Patients who sign the informed consent form.
- **Excluded Subjects:** Subjects who are enrolled but never undergo insertion of the study catheter. Excluded subjects will only be followed between ICF signature and exclusion for event reporting.

- **Evaluable Subjects**: All enrolled subjects who have the study catheter inserted.
- **Discontinued Subjects**: Enrolled subjects who have the study catheter inserted but do not undergo ablation (i.e., no RF energy is delivered with the study catheter). Discontinued subjects will remain in follow-up for 30 days.
- **Lost to Follow-up Subjects:** Evaluable subjects of which contact is lost after most recent visit (despite 3 documented attempts to contact the subject).
- **Withdrawn / Early Termination Subjects:** Subjects who withdraw consent for study participation or are withdrawn by the investigator, are terminated from the study prior to completion of all follow-up visits.
- **Completed Subjects:** Enrolled subjects who have not been excluded, discontinued, expired, withdrawn, terminated early, or lost-to-follow-up from the study prior to the final study visit.

5. Responsibilities

5.1. Investigator Responsibilities

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

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

- Inform the appropriate entities (e.g., Sponsor, CA, EC) in a timely manner regarding the occurrence of AEs and/or product malfunctions.
- Making sufficient effort to maintain contact with treated subjects who fail to comply with the follow-up requirements
- Maintain study records for at least 5 years or as specified per country specific record retention requirements after the study is completed and or terminated. The Sponsor will notify the Investigator of either of these events.
- Complying with EC and Sponsor annual report requirements, including the final report.

5.2. Sponsor Responsibilities

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

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

6. Study Device Description

6.1. Device Acquisition

After obtaining a fully executed clinical trial agreement and appropriate EC approvals, the sponsor will 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. Investigators are responsible for appropriate logging of the devices received, verification of packing slip information (i.e., lot numbers and quantity shipped), date and identity that each device was used in the study, disposition information regarding disposal or return to the Sponsor.

6.2. Device Storage and Stability

Devices are to be stored in a secure/locked location and in accordance with the IFU. Do not use this device after the "Use By" date.

6.3. Device Preparation

Information related to device preparation can be found in the Instruction for Use.

6.4. Instructions for Use

A comprehensive set of IFU/User manual for the Study Devices (Catheter and Generator) and all accessory cables/interface cables is contained in each product package and is also available upon request.

6.5. Device Description

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

Table 2 Required Study Devices

Investigational Devices	Function
THERMOCOOL SMARTTOUCH® SF-5D Catheter [redacted]	Delivers RF energy to the target tissue.
nMARQ™ Multi-Channel RF Generator [redacted]	Transmits RF energy to the THERMOCOOL SMARTTOUCH® SF-5D Catheter
Devices/Standard Equipment	**Function**
THERMOCOOL SMARTTOUCH® SF-5D interface cables [redacted]	Provides connection between the THERMOCOOL SMARTTOUCH® SF-5D Catheter, and the THERMOCOOL SMARTTOUCH® SF-5D Dongle
8.5 F. compatible sheath (Agilis, SL0™, SL1™, MOBICATH, VIZIGO™)	Providing guidance and support during the procedure.
COOLFLOW® Irrigation Pump	Delivers heparinized saline to THERMOCOOL SMARTTOUCH® SF-5D Catheter electrodes for cooling during the RF energy application
Indifferent electrode compatible with nMARQ™ System	Component of the RF current return path
THERMOCOOL SMARTTOUCH® SF-5D Dongle (EM-5050-055F)	Provides three-point connection between the THERMOCOOL SMARTTOUCH® SF-5D Catheter, the nMARQ™ Multi-Channel RF Generator, and the Patient Interface Unit (PIU) of the CARTO® 3 EP Navigation System
CARTO® 3 v 6 System	For mapping and visualization information. Version 6.0

7. Study Medication

The following medications are recommended/required (as indicated) for subjects undergoing a study catheter ablation for AF.

- **Before the AF Ablation procedure**
  - Uninterrupted systemic anticoagulation therapy is recommended for at least 3 weeks prior to the AF ablation procedure.

- **During the AF Ablation procedure**

  - Administer a heparin bolus PRIOR to transseptal puncture.
  - Target an ACT of 300-400 seconds prior to inserting the study catheter and throughout the procedure.
    - It's strongly recommended to check ACT levels on regular basis during the procedure to ensure an ACT target of 300-400 seconds.

- Adenosine: A bolus (i.e. 24 mg) to confirm PV isolation; rule out dormant conduction
  OR
- Isoproterenol to achieve a ≥ 20 beats per minute increase in heart rate to induce AF upon completion of the ablation procedure is recommended if pacing maneuvers are not performed (recommended dose range is 2-20 mcg/min).

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

8. Study Schedule

8.1. Screening and Informed Consent

Subjects presenting to the institution with symptomatic PAF and considered for an RF ablation procedure should be screened by the investigator or designated member of the research team for study eligibility per the protocol inclusion and exclusion criteria. Sites will be instructed to screen all subjects who require a documented RF ablation procedure for symptomatic PAF without regard to sex or race.

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

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

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

8.2. Baseline Evaluation and Procedures

8.2.1. *Pre-Procedure/Baseline Assessments*

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

- **Patient Information and Consent** (procedure must be done within 60 days of consent)
- **Demographics** (age, gender, etc.).
- **Medical history,** including but not limited to arrhythmia, heart disease, thromboembolic events, lung/respiratory problems.
- **AF history** (first evidence of AF, number of episodes, symptoms, etc.).
- **Medication history**: Medication history (cardiac medication, AAD medication, anticoagulation regimen and any other clinically significant medication history) shall be gathered by interview or from medical records following enrolment but prior to the ablation procedure and should be recorded in the eCRF.
- **Anticoagulation therapy:** Uninterrupted systemic anticoagulation therapy is recommended for at least 3 weeks prior to the AF ablation procedure.
- **CHA2DS2 VASc Score**: Subjects will be scored against the CHA2DS2 VASc.
- **NYHA** Functional Class Scale.
- **Pregnancy test** must be done on all women of childbearing age and potential, within 1 week prior to the procedure and documented in the subject's medical chart.
- **Transthoracic Echo (TTE)** to determine the atrial size and LVEF% should be completed within 30 days prior to the study ablation procedure, unless the subject has undergone an imaging procedure within 6 months prior where the atrial size was assessed.
- Imaging for **detection of left atrial thrombus** or other structural contraindications to an ablation procedure is mandatory the day before or the day of the ablation procedure. Presence of a thrombus will require postponement of the ablation procedure or may even lead to exclusion of the subject from further study involvement. The imaging method to be used for atrial thrombus detection is transesophageal echocardiography (TEE), intracardiac Echocardiography (ICE), Computed Tomography (CT) or Magnetic Resonance Imaging (MRI).
- **Electrocardiogram** (12-Lead ECG). Data from 12-lead ECG recordings will be collected if available.
- **Adverse Events** must be collected from the time the subject signs the informed consent onwards
- **Cerebral MRI, Neurological Exam and Neurological Evaluation using the Montreal Cognitive Assessment (MoCA), NIH Stroke Scale (NIHSS) and Modified Rankin Scale (mRS)** are required to be performed within 72- hours pre-procedure to evaluate the neurological condition and presence of neurological deficits of the subjects before undergoing study ablation procedure. A certified/qualified physician expert must perform neurologic exams at pre- and post-ablation and possibly at other follow-up visits, pending previous findings of micro-emboli/neurologic deficits.

8.2.2. *Study Ablation Procedure Guidelines*

8.2.2.1 Recommended Ablation Parameters

In this study protocol, TGA RF energy application mode [redacted]) is to be used as the primary mode for circumferential pulmonary veins isolation. Only after the investigator deems TGA unable to achieve PVI should the study catheter in Q-mode be used to complete the procedure.

[redacted]

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

[redacted]

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

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

[redacted]

Recommended Contact Force (CF) Settings

[redacted]

8.2.2.2 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 monitoring:

- Use of an esophageal temperature probe
- Esophageal visualization with CARTOSOUND® and/or ICE
- Esophageal visualization using barium swallow
- Esophageal displacement during RF application

8.2.2.3 Study Ablation Procedure Sequence

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

The **AF ablation procedure** for this study should follow this **sequence**:

- Transseptal puncture
- Mapping (left atrial anatomical map) is required prior to the ablation procedure.
  Note: An anatomical map is not required for triggers outside the left atrium (e.g. SVC/CS etc.)
- Ensure Esophageal monitoring
- Confirmation of target ACT 300-400 PRIOR to insertion of the study catheter into the left atrium and maintain throughout the procedure
- Introduction of the study catheter
- Complete PV encirclement with TGA mode as the primary mode for ablation (refer to NOTE 1 below). Q-mode can be used where the investigator deems TGA mode unable to achieve PVI.
- Confirmation of PV isolation in all targeted PV's
- Waiting period (20 minutes) and Isoproterenol/adenosine challenge
- Confirmation of entrance block in all targeted PV's

8.2.2.4 Study Ablation Procedure Guidelines

In this study protocol, TGA mode is to be used as the primary mode for pulmonary vein isolation (refer to NOTE 1 below). Only after the investigator deems TGA mode unable to achieve PVI should the study catheter in Q-mode be used to complete the procedure. (refer to appendix A for Q-mode)

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**.

General Introduction of the Study Catheter

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

- When ablating near the esophagus (along the posterior wall of the left atrium), take precautions to avoid injuring the esophagus (see section 8.2.2.2 for required esophageal monitoring instructions)
- Prior to ablation in the region of the right superior PV, precautionary measures are recommended to evaluate proximity to the phrenic nerve, such as pacing maneuvers

Electrophysiology Study, Mapping and Ablation procedure

- Anesthesia or sedation should be delivered per standard EP lab procedure.
- Placement of diagnostic catheters:
  - Coronary sinus catheter in the CS for pacing purposes
  - Other catheters may be placed at the discretion of the investigator
- Mandatory use of an esophageal monitoring method to minimize risk of esophageal injury.
- Administration of heparin bolus prior to transseptal puncture
- Transseptal puncture

- Following successful transseptal puncture, an anatomic map can be performed, utilizing Lasso® or Pentaray® (or other at investigator discretion)
- Confirm target ACT 300s-400s. Systematic Anticoagulation with heparin should be administrated with ACT level checked to target ACT of 300-400 seconds throughout the procedure
- Introduce the study catheter (if not yet used for mapping purposes)
- Perform respiratory training
- Use the AUTOTAG feature in Carto to tag each TGA mode ablation point after each application
- Display Visitag prior to the ablation to ensure stability
- A pre-ablation flow rate delay of minimal 2 seconds will occur before every RF application
- Ablation: RF power application [redacted] (TGA-mode)
- A post-ablation flow rate delay of minimal 4 seconds will occur after every RF application
- TGA mode should be used for full PV encirclement (refer to NOTE 1 below). Only in case the investigator deems TGA mode unable to achieve PVI should the study catheter in Q-mode be used to complete the procedure.
- Move the catheter to a new location (~4mm) if clinically effective ablation is achieved (refer to NOTE 2 below)
- At the new location **ensure catheter stability** before commencing RF application.
- Continue RF applications and catheter movement until the circumferential PVI is completed.
- Precautions:
    - If the temperature increases above the temperature cutoff [redacted] RF application will stop immediately (automatically)
    - The decision to interrupt RF power delivery at any time during ablation should be guided by Clinical Investigator judgment and the monitoring of ablation effectiveness parameters commonly used such as EGM reduction and/or impedance changes.
- All subjects will continue PV ablation until PVI is achieved and isolation is confirmed by Lasso® or PentaRay® (or other at investigator discretion).
- After PVI is confirmed, initiate a 20-min waiting period (ref. section verification of ablation procedure).
- Map the ablation lines with a mapping catheter (Lasso® or PentaRay® or other at investigator discretion)
- Perform additional applications, if required
- Administer adenosine or isoproterenol for each targeted PV to rule out dormant conduction.
- Perform additional applications (touch-up), if required
- Confirmation of entrance block of all targeted PV's

NOTE 1: The recommendations provided in this section are based on data obtained from animal studies. Use clinical judgment when using this catheter paying careful attention to initial impedance, impedance drop, electrogram reduction, time of RF application, and with consideration of individual patient conditions when selecting settings

NOTE 2: At the end of a TGA ablation ([redacted] a second [redacted] RF application can be made at the same ablation spot if clinically effective ablation did not occur. A 4-sec waiting period before a new TGA RF application at the same site is required.

Ablation outside the PV Ostia

- Prophylactic ablation of empirical sites outside the PV Ostia is discouraged for this protocol
- CFAE ablation is not allowed per protocol
- In the event of typical AFL/ AT, the placement of linear lesions in the cavotricuspid isthmus (CTI) is at the discretion of the investigator
- If linear lesions are placed, bidirectional block should be confirmed as demonstrated by mapping and/or pacing maneuvers

Verification of ablation procedure

- Verification of isolation of the targeted PVs by demonstrating entrance block into each targeted PV is required. To verify entrance block, analyze electrograms in sinus and/or atrial paced rhythm to confirm that no PV potentials are present.
- After initial PVI confirmation, apply a 20-minute waiting period. The time of initial PVI confirmation must be documented in the medical record as source documentation.
- Mapping the ablation lines during the 20-minute waiting period should occur per standard practice. If conduction is noted during mapping, additional RF applications should be applied.
- After the 20-minute waiting period, administer one of the below to rule out dormant conduction:
    - Isoproterenol (to achieve a ≥ 20 beats per minute increase in heart rate; recommended dose range is 2-20 mcg/min)

  OR
    - Adenosine (i.e. bolus of 24 mg to confirm PV isolation)
- In case of acute reconnection being identified, apply touch-up applications until entrance block is re-confirmed
- Final demonstration of entrance block **MUST** be confirmed and documented by Lasso® or PentaRay® catheter (or other at investigators discretion)
- The ablation procedure is considered complete when confirmation of entrance block/isolation of the pulmonary veins is confirmed and documented after the 20-minute waiting period and isoproterenol/adenosine challenge.

8.2.3. *Data collection during study ablation procedure*

Procedural data collection will be done through generator files, CARTO® datafiles, procedural worksheets and subject medical files. Documentation of procedural data will be kept in the subject's CRF, back-up generator files and back-up CARTO® data files for study 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 patient binders, and one fully anonymized copy will be sent to the sponsor, in a timely manner

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

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

- RF application-mode per lesion (TGA-mode/Q-mode/other)
- Number of RF applications with QDot catheter (total/Q-mode/TGA-mode) and with non-study catheter
- Duration of RF applications with QDot catheter (total/Q-mode/TGA-mode) 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 (if captured); fluid output and net fluid input (if captured)
- Strategy used to minimize risk of esophageal injury
- Abnormal esophageal temperature rises (if captured)

8.2.4. *Pre-Discharge Assessments*

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

- **Cardiac medication and anticoagulation regimen** (only cardiac related AADs, anticoagulation regimen, etc.)
- **ECG** in case of standard of care
- **Endoscopy**: imaging of the esophagus for the detection of esophageal injury within 72 hours post-procedure; prior to discharge.
- **Transthoracic echocardiogram (TTE)** to assess the pericardium. In the event of a significant pericardial effusion is identified, subjects should be followed until the condition resolves.
- **Adverse events**, if any
- **Occurrence of AF** or other arrhythmias, if any
- **Cerebral MRI** (within 72hours post procedure), Neurological exam and Neurological Evaluation using the NIH stroke Scale (NIHSS) within 72- hours post procedure, prior to discharge. A certified/qualified physician expert must perform neurological exams.

8.2.5. *Repeat Ablation Procedures*

Repeat ablation procedures and management of arrhythmia recurrences during follow-up may be performed at the discretion of the investigator. Repeat procedures during follow up may be managed per investigator discretion using a commercially approved and available ablation catheter. It's recommended to perform repeat ablations with the THERMOCOOL SMARTTOUCH® SF-5D system. The follow-up schedule will remain based on the initial ablation procedure.

8.3. Post-Ablation Follow-up Schedule

The subject will be required to complete follow up visits through 3 months post initial ablation procedure. Follow-up will be done at 7 days (phone call or clinic visit), 1 month (if applicable) and 3 months (clinic visits).

Discharged subjects will receive a telephone call or have a clinic visit at 7 days (7D, day 6-8) post ablation procedure to assess cardiac medication AFL/AF/AT occurrences and occurrence of (Primary) Adverse Events.

The subject will be required to complete follow up through 3 months post initial ablation procedure. The follow-up visits are 1 month ± 7 days (1M, day 23-37) (if applicable) and 3 months ± 14 days (3M, day 76-104) post ablation procedure. Follow-up visit schedule should be based on the date of the index study ablation procedure and will not reset if subject undergoes a repeat AF ablation procedure.

- If findings of micro-emboli/neurologic deficits/ CVA or TIA events identified at a prior evaluation (i.e. pre-discharge) a **1 month follow up visit** will be performed with the following assessment:
  - **Cerebral MRI**, Neurological Exam and NIH Stroke Scale (NIHSS), MoCA and mRS assessments. Subjects with findings of micro-emboli/neurologic deficits/CVA/TIA will undergo additional MoCA/mRS through 3M follow-up

- At the **3 months post ablation procedure visit** (clinic visits) the following assessments should be performed:
  - **Cardiac medication and anticoagulation regimen** (only cardiac related AADs, anticoagulation regimen, etc.)
  - Medical / Hospitalization History
  - **NYHA** Functional Class Scale.
  - **ECG** in case of standard of care
  - **Adverse events**, if any
  - **AFL/AT/AF occurrence** and repeat ablation
  - **Cerebral MRI**, Neurological Exam and NIH Stroke Scale (NIHSS) and MoCA/mRS assessments will be performed in case observations findings of micro-emboli/neurologic deficits were noted during previous assessments. A certified/qualified physician must perform neurologic exams at pre-and post-ablation and possibly at other follow-up visits, pending findings of micro-emboli/neurological deficits.
  - **End of Study** Follow up

8.4. Final Study Visit

The Final Study visit for each participant will be conducted 3 months ± 14 days post ablation procedure.

8.5. Early Termination Visit

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

8.6. Unscheduled visit

If subject returns for a potential study related cardiovascular or neurological visit outside of the protocol-defined visit schedule provided in Table 4, the visit will be considered "unscheduled" (UNS). An investigator may request an unscheduled visit in the presence of a new or worsened 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 per clinical investigational plan.

8.7. Core Laboratory for Evaluation

No core lab will be used during this study

8.8. Schedule of Events Table

This table displays the required schedule for subject treatments and evaluations

Table 3 Summary of Subject Assessments

Assessments	Pre-ablation	Pre-discharge	7D (D6-8)	M1 (D23-37)	M3 (D76-104)	UNS
Clinic visit	●			● [9/10]	●	●
Phone Call			● [1]			
Patient Informed Consent[2]/Demographics	●					
Medical/AF history	●					
Cardiac Medication and anti-coagulation Regimen	●	●	●	● [9]	●	●
CHA2DS2-Vasc Score	●					
NYHA functional Class Scale	●				●	
Pregnancy Test	● [3]					
Transthoracic Echo (TTE)	● [4]	●				
LA thrombus detection	● [5]					
ECG	● [5]	● [6]			● [6]	● [6]
Adverse events	●	●	●		●	●
AFL/AT/AF occurrence and repeat ablation		●	●		●	●
Endoscopy		● [8]				
Cerebral MRI	● [7]	● [8]		● [9]	● [9]	● [10]
Neurological Exam	● [7]	● [8]		● [9]	● [9]	● [10]
NIH Stroke Scale	● [7]	● [8]		● [9]	● [9]	● [10]
mRS	● [7]			● [9]	● [9]	● [10]
MoCA	● [7]			● [9]	● [9]	● [10]

1. May be substituted with a clinic visit.
2. To be completed within 60 days prior to ablation procedure
3. In all women of childbearing age and potential. To be completed within 1 week prior to ablation procedure.
4. To be performed within 30 days prior to procedure to determine the LA size and LVEF%, 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.
5. To be completed the day before or the day of the study ablation procedure. Imaging modality TEE, ICE, CT or MRI.
6. To be collected if completed as standard of care.
7. To be completed within 72-hours pre-procedure.
8. To be completed within 72-hours post-procedure.
9. To be undertaken/collected if neurologic symptoms and/or new cerebral ischemic lesions identified/CVA/TIA reported in a prior evaluation.
10. To be completed only if a previous mandated test was missed, or if subject reports neurologic difficulties between scheduled follow-up visits and unscheduled assessment per investigator approval

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9. Assessment of Safety

9.1. Specific Safety Parameters

9.1.1. *Definition of Adverse Events (AE)*

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

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

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

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

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

- Minor pericarditis attributable to the ablation procedure defined as pleuritic chest discomfort with or without pericardial rub and ECG changes.
- AF/AFL/AT recurrence requiring pharmacological or synchronized electrical cardioversion during the hospitalization for the index ablation procedure, or throughout the duration of the study. However, new onset of left atrial flutter occurring post-ablation is an AE. Re-ablation for AF or preexisting AFL/AT itself is not an AE, however any procedural complication is considered an AE and shall be reported within the applicable timelines.

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

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

- Leads to a death
- Leads to a serious deterioration in the health of a subject that resulted in:
  - A life-threatening illness or injury
  - An injury or permanent impairment of a body structure or a body function
  - In-patient hospitalization or prolongation of an existing hospitalization*
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function
- Leads to fetal distress, fetal death or a congenital abnormality or birth defect.

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

9.1.3. *Primary Adverse Event (PAE)*

A **Primary AEs** is an event listed in Table 4 which occurs within the first week (7 days) following an ablation procedure. Primary AEs are considered SAEs.

Table 4 Primary Adverse Events

Primary Adverse Event	Description / Criteria
Atrio-Esophageal Fistula*	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 the index AF ablation procedure. A significant pericardial effusion is one that results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1cm or more pericardial effusion as documented by echocardiography Cardiac tamponade/perforation should also be classified as: Early – diagnosed prior to discharge Late – following initial discharge from the hospital
Death*	Subject death directly related to the device or procedure and occurs at any time during or after the procedure.
Major Vascular Access Complication /Bleeding	Major Bleeding: Requires and/or treated with transfusion or results in a 20% or greater fall in hematocrit. Major Vascular Access Complication: Defined as a hematoma, an AV fistula or a pseudoaneurysm which requires intervention such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission.
Myocardial Infarction	Presence of any one of the following criteria: – Detection of ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]) that persist for more than 1 hour – Development of new pathological Q waves on ECG – Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Phrenic Nerve Paralysis	Absent phrenic nerve function as assessed by a sniff test, and associated with symptoms of dyspnea and orthopnea (diagnosed by chest x-ray). A phrenic nerve paralysis is considered to be permanent when it is documented to be present 12 months or longer following ablation. Under this protocol, diaphragmatic paralysis/phrenic nerve palsy will be considered a Primary AE if specified symptoms have not improved at the 3-month final visit

Primary Adverse Event	Description / Criteria
Pulmonary Vein Stenosis*	A reduction of the diameter of a PV. Severe PV stenosis (≥70% reduction in the diameter of the PV) will be considered a primary adverse event and major complication of AF ablation.
Stroke/Cerebrovascular Accident (CVA)	Diagnosis: -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) Definition: 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
Transient Ischemic Attack	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 h), always within 24h; neuroimaging without tissue injury.
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.

* Device or procedure related death, atrio-esophageal fistula and pulmonary vein stenosis that occur greater than one week (7 days) post-procedure shall be deemed Primary AE.

** Hemodynamic compromise or instability is defined as Systolic blood pressure < 80 mmHg

† Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.

†† mRS assessments should be made by qualified individuals according to a certification process. If there is discordance between the 30 and 90 day mRS, a final determination of major versus minor stroke will be adjudicated by an independent physician/committee.

9.1.4. *Adverse Device Effect (ADE) / Serious Adverse Device Effect (SADE)*

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

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

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

9.1.5. *Unanticipated (Serious) Adverse Device Effect (UADE/USADE)*

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

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

9.1.6. *Study Device Deficiency, Failure or Malfunction*

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

9.2. Classification of an Adverse Event

9.2.1. *Severity of Event*

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

Table 5 Intensity or Severity Definitions

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

9.2.2. *Relationship to Study Device*

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below, based on MEDDEV 2.7/3 Rev.3.

Table 6 Adverse Event Causality Classifications

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

9.2.3. *Outcome*

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

Table 7 Adverse Event Outcome Classifications

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

9.2.4. *Expectedness*

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

Potential adverse events that are reasonably anticipated to occur during the cardiac electrophysiology procedure are listed in Table 8. These events should be reported via EDC as anticipated AEs. Anticipated adverse events are to be reported to the sponsor via EDC as indicated in section 9.4.

Table 8 A provides a comprehensive list of anticipated AEs.

Anticipated Adverse Events	
Acute Respiratory Distress Syndrome (ARDS)	Air embolism
Allergic reaction	Allergic reaction to Anesthesia (e.g., hair loss)
Anaphylactic shock	Anemia
Anesthesia reaction	Apnea - sedation induced
Arrhythmia: bradycardia	Arrhythmia: pro-arrhythmias
Arrhythmia: tachycardia	Aspiration pneumonia
Asthmatic attack	Atelectasis
Atelectasis	Atrial fibrillation*
Atrio-Esophageal fistula	Atypical left atrial flutter
AV fistula	Bleeding complications
Bleeding requiring transfusion	Cardiac arrest
Cardiac perforation	Cardiac thrombo-embolism
Cerebro-vascular accident (CVA) / stroke	Chest pain/discomfort
Complete heart block, temporary or permanent	Conduction block: ongoing / resolved
Congestive Heart Failure	Coronary artery dissection
Coronary artery occlusion	Coronary artery spasm
Coronary artery Thrombosis	Damage to the vascular system
Death	Deep venous thrombosis
Diaphragmatic paralysis	Dislodgement of permanent pacing leads
Disseminated Intravascular Coagulation	Dyspnoea
Endocarditis	Epistaxis
Esophageal Injury	Exacerbation of pre-existing arrhythmia*
Expressive aphasia	Fainting
Fatigue	Gastric reflux
Gastrointestinal diverticulosis	Gastro-intestinal NOS
Heart Failure	Hematoma (local) /ecchymosis
Hemorrhage	Hemothorax
High / increased creatine phosphokinase (CPK)	Hypotension
Hypoxia	Increase in frequency or duration of episodes of typical atrial flutter
Increased phosphokinase level	Infection, localized

Infection, systemic	Injury to skin, muscle, connective tissue due to body position, electrical cardioversion, etc.
Laceration	Leakage of air or blood into the lungs or other organs due to perforation
Liver toxicity	Mobile strands in Inferior Vena Cava
Myocardial Infarction	Nausea
Neurological disorders (headache)	Neurological disorders (poor coordination)
Neurological disorders (tremor)	Obstruction to the vascular system
Palpitations	Perforation to the vascular system
Pericardial effusion without tamponade	Pericardial effusion resulting in tamponade
Peripheral embolus	Pericarditis
Peripheral thromboembolism	Peripheral nerve injury
Phrenic nerve damage	Phlebitis
Pneumothorax	Pleural effusion
Pulmonary edema	Pseudoaneurysm
Pulmonary hypertension	Pulmonary embolism
Pulmonary vein dissection	Pulmonary toxicity, like acute pulmonary syndrome
Pulmonary vein thrombus	Pulmonary vein Stenosis
Renal failure	Pump failure
Respiratory failure	Respiratory depression
Rhabdomyolysis, including produced by body position or propofol	Retroperitoneal hematoma
Seizure	Sedation induced CO_2 retention with lethargy and cholecystitis
Skin burns (due to cardioversion, tape, etc)	Sepsis
Skin injury / muscle or connective tissue injury due to body position, electrical cardioversion	Skin discoloration
Tamponade	Skin rash
Thrombocytopenia	Temperature elevation
Thrombosis	Thromboembolism
Transient extremity numbness	Thyroid disorders
Unintended complete or incomplete AV, Sinus node, or other heart block or damage	Transient ischemic attack (TIA)
Urinary tract injury or infection related to the urinary catheter	Urinary retention
Vasovagal reactions	Valvular damage/insufficiency
Volume overload	Vision change
X-ray radiation injury of skin, muscle and/or organ	Worsening obstructive, restrictive, or other form of pulmonary disease

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

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

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

All AE/SAEs need to be followed until the event is resolved (with or without sequelae). The medical monitor or designee of this clinical investigation will decide if more follow up information is needed in case the event is not resolved at study completion. All required treatments and outcomes of the SAE must be recorded in the eCRF.

9.4. Reporting Procedures

9.4.1. *Adverse Event Documentation and Reporting Requirements*

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

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

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

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

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

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

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

Table 9 AE Reporting Requirements

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

9.4.2. *Serious Adverse Events Reporting*

All SAEs, whether or not they are related to the device or procedure, **must be reported** to the Sponsor, via eCRF, **immediately upon awareness of event but no later than 72 hours** by the study site personnel.

The study investigator shall report the SAE and device deficiencies that could have led to SAE to the reviewing EC in accordance with the local EC requirements. The Sponsor will ensure that investigators are instructed to return devices suspected of causing an AE or SAE (i.e., definitely device-related or possibly device-related) in accordance with relevant regulations and current company procedures.

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

The sponsor will submit as per site specific requirements to all participating clinical investigators, an update of all SAEs and all device deficiencies that could have led to a SAE occurring to all participating sites. Event reporting to relevant regulatory authorities for non- CE marked devices per MEDDEV 2.7/3 Rev3 guidelines will occur by the sponsor and if indicated per local country requirements by the investigator. Pursuant to EN ISO 14155: 2011 all SAEs will be fully recorded and reported by the sponsor to the regulating Ministry of Health (MOH) as well as the EC according to the deadlines in force.

9.4.3. *Unanticipated Device Effect Reporting*

All UADE/SADE/USADE **must be reported** to the Sponsor, via eCRF, **immediately upon awareness of event but no later than 72 hours** by the study site personnel. An investigator shall submit to the reviewing EC a report of any unanticipated adverse device effect occurring during an investigation according to EC requirements.

9.4.4. *Events of Special Interest*

All study device failure/malfunction **must be reported** to the Sponsor, via eCRF, as soon as possible within **72 hours** by the study site personnel. If a device failure is detected or suspected, it should be documented on the eCRF and the device returned according to the Sponsor's instructions.

The investigational device should be sent to appropriate R&D team or designated Quality engineer and should be reported to the medical safety lead. Complaints related to non-investigational products manufactured and/or distributed by Biosense Webster, used during the procedure related to other devices (other than the study device under investigation), are to be reported according to current Biosense Webster procedures and other policies as necessary (i.e., institutional policies, EC policies, and local regulations), investigators are instructed to return devices in accordance with current company procedures and other relevant regulations.

Event reporting to relevant competent authorities in accordance with the jurisdictional regulations will occur by the sponsor and/or by the investigator, depending upon the local requirements and will be done in EU per MEDDEV 2.12/1 guidelines for CE-marked devices manufactured by Biosense Webster and per MEDDEV 2.7/3 guidelines for non-CE-marked devices manufactured by Biosense Webster.

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

9.5. Safety Oversight

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

10. Administrative Responsibilities

10.1. Ethics Committee and Competent Authority Application

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

In addition, Biosense Webster, Inc. is responsible for notifying the relevant CA of the intention to perform a clinical investigation under this protocol and ensure to get the official response/ approval before starting the clinical investigation.

10.2. Audits and Inspections

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

11. Deviations from the Clinical Study Plan

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

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

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

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

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

12. Investigational Product Accountability

12.1. Use of the Investigational Device and Investigator Experience

In addition to the clinical protocol training (i.e. during the site initiation visit), all investigators who will be performing the ablation procedures for this study will be required to attend both a didactic session, which includes detailed reviews of the study catheter (specifications, parameters, etc.) and the results of the preclinical studies completed. Ablating physicians with no prior in human experience with multi-ablation catheter will also receive hands-on training using the THERMOCOOL SMARTTOUCH® SF-5D catheter. The combination of the didactic and hands-on (in-vitro and/or in-vivo) portions of the documented device training will provide the investigator with the experience necessary to perform the protocol specified procedures for the study.

Investigators selected will be highly skilled in intracardiac mapping and AF ablation with RF ablation catheters.

12.2. Materials

Biosense Webster, Inc., Irwindale, CA USA, has manufactured the catheters to be used in this study. The investigational devices were built in a clean room environment, and sterilized using EtO gas, in a manner similar to standard, commercially approved Biosense Webster products.

Complete manufacturing records of every lot of catheter manufactured for human use during this study are maintained at Biosense Webster, Inc. Each lot of catheters is released for human use under a Confirmation of Conformity from Regulatory Affairs that will certify that the investigational catheters conforms to the Essential Requirements for product release apart from those features that are being investigated in this clinical investigation. And that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient.

12.3. Device Acquisition and Accountability

After obtaining a fully executed clinical trial agreement and appropriate competent authority (CA)/ethical committee (EC) approvals, the study site will receive the necessary amount of study-related materials prior to commencement. Study-related devices (investigational 'THERMOCOOL SMARTTOUCH® SF-5D catheters' and non-investigational devices) will be shipped to the site upon completion of required documentation.

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

The Sponsor will keep records of all investigational devices shipped to the site.

Investigational site personnel is responsible for appropriate logging of devices received, verification of packing slip information (i.e. lot numbers and quantity shipped) and date, and identifying that each device was used in the study and disposition information completed when returned to the Sponsor. The Sponsor will label all investigational devices as "Investigational device" in a prominent location.

The Investigational Device Accountability Log shall record the following information:

- Date of receipt
- Person in receipt of the devices
- Quantity received
- Catalog number for catheters
- Serial/lot numbers
- Expiry Date
- Date devices was used
- Subject ID on whom device was used
- Date of return

12.4. Device Returns

All investigational devices 'THERMOCOOL SMARTTOUCH® SF-5D catheters' (**used and unused**) will be returned to the Sponsor's attention at the below address. Any suspected malfunctioning device or device associated with an adverse event (device related or possibly device related) will undergo a thorough complaint analysis and must be properly documented on the electronic case report form (eCRF).

All returned devices must be properly labeled with the subject identification number, date of issue, identified as a defective return, non-defective return, or adverse event (as applicable).

All tracking information must be retained in the event the package has been lost and requires tracking. All investigational devices should be returned to:

ATTN: Complaints Lab
Biosense Webster, Inc.
15715 Arrow Highway
Irwindale, CA 91706 USA

12.5. Device Labeling

Sample labels are included in the package approved by the Regulatory/Competent Authorities. All labeling clearly identifies the product as investigational.

13. Clinical Monitoring

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 Sponsor representative, qualified to perform such visit.

Monitoring visits may include, but are not limited to, the following:

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

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

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

14. Statistical Methodology

14.1. Study Design

The QDOT-FAST study is a prospective, multi-center, non-randomized, interventional clinical study.

14.2. Treatment Assignment

All subjects in the study will be treated with the THERMOCOOL SMARTTOUCH® SF-5D Catheter (D-1395-05-SI).

14.3. Interval Windows

See Section 8.8.

14.4. Primary and Secondary Endpoints, and Associated Hypotheses

14.4.1. *Primary Endpoints and Associated Hypotheses*

The primary safety endpoint is acute safety defined as the Primary Adverse Events (PAEs) within the first 7 days. PAEs include the following AEs:

Atrio-Esophageal Fistula*	Phrenic Nerve Paralysis
Cardiac Tamponade/perforation	Pulmonary Vein Stenosis*
Death*	Stroke/CVA
Major Vascular Access Complication/Bleeding	Thromboembolism
Myocardial Infarction	TIA

*Device or procedure related death, pulmonary vein stenosis and atrio-esophageal fistula that occur greater than one week (7 days) post-procedure are considered and analyzed as primary AEs.

The primary effectiveness endpoint is acute procedural success defined as achieving confirmation of entrance block in all targeted PVs after adenosine and/ or isoproterenol challenge. The use of non-study catheter for PVI will be considered as an effectiveness failure.

No formal statistical hypotheses will be formulated and performed for the primary endpoints.

14.4.2. *Secondary Endpoints and Associated Hypotheses*

No formal statistical hypotheses will be formulated and performed for the secondary endpoints. The secondary safety and procedural endpoints are listed below.

Safety

- Incidence of Serious Adverse Device Effects (SADEs)
- Incidence of Serious Adverse Events (SAEs) within 7 days (early-onset), >7-30 days (peri-procedural) and >30 days (late onset) of initial ablation procedure
- Incidence of non-serious adverse events
- Incidence of pre-and post-ablation asymptomatic and symptomatic cerebral emboli as determined by MRI evaluations
- Incidence of new or worsening neurological deficits compared to baseline
- Summary of NIHSS, mRS and MoCA scores at baseline and follow-up timepoints

Effectiveness

- PVI achieved with TGA mode only among all targeted veins and by subject
- PVI achieved with combined use of TGA and Q-mode among all targeted veins and by subject
- Ablation of acute reconnection (touch-up) among all targeted veins and by subject
- Touch-up applications with TGA, Q-mode and non-study catheter applications
- PV ablation by a non-study catheter among all targeted veins and by subject

Additional analyses on procedural data, including but not limited to:

- Use of QDOT Micro™ catheter ablation outside the PV area
- Use of a non-study catheter for ablation outside the PV area
- Total procedure time, mapping time, PV ablation time, total ablation time, RF application time, LA dwell time
- Total number of RF applications, % TGA applications and % Q-mode applications
- Anatomical location of touch-up applications
- Temperature, power, contact force, impedance
- Total Fluoroscopy time/dose

14.5. Levels of Significance

There are no formal hypothesis tests for this study. All confidence intervals will use two-sided 95% confidence unless otherwise stated.

14.6. Analysis Sets

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

- **Safety Population**: The safety population will include all enrolled subjects who have the investigational device inserted, regardless if RF energy is delivered.
- **Effectiveness Population**: The effectiveness population will include all enrolled subjects who have had the investigational device inserted and underwent ablation with the study catheter used in conjunction with TGA mode for PVI. The subjects without any TGA mode application for PVI will be excluded from the effectiveness population.
- **Neurological Assessment Evaluable (NAE) Population:** The NAE Population will include all enrolled subjects who meet the eligibility criteria, have been treated with the study catheter and had any post-ablation neurological assessment. Assessment of incidence of new lesions or deficits requires availability of the associated pre-procedural assessment.

14.7. Sample Size Justification

This is a clinical feasibility study for evaluation of safety and acute performance of THERMOCOOL SMARTTOUCH® SF-5D system with TGA mode application for PVI. This clinical investigation is intended to provide preliminary estimates of workflow and acute outcomes. Enrollment in the clinical investigation will be 50 subjects, distributed over up to 10 centers in Europe. Minimum attrition is expected for safety assessment. No more than 10% attrition is expected to assess effectiveness outcomes.

Because this study is a feasibility study, there is no statistical power calculation and no hypothesis to be tested. 50 subjects are deemed sufficient to clinically characterize safety and acute outcomes.

14.8. Analyses to be conducted

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

14.8.1. *General Conventions*

Standard descriptive summaries for continuous data include the number of observations with data, mean, standard deviation, median, minimum, and maximum values. For categorical data, the count and percent will be provided. Percentages will be based on the number of subjects without missing data.

14.8.2. *Disposition of Study Subjects*

Subject disposition will be summarized for all enrolled subjects by summary tables and listings.

14.8.3. *Demographic and Baseline Characteristics*

All demographic and baseline characteristics, procedural, and immediate post-operative details will be summarized and listed overall in the safety population.

14.8.4. *Primary and Secondary Endpoint Analyses*

14.8.4.1. *Analyses of Primary Safety Endpoint*

- **Primary Safety Endpoint:** Primary safety outcome will be reported as primary adverse events (within 7 days of catheter ablation, with exception for PV stenosis and AEF). The number of events and the number and percentage of subjects experiencing primary adverse events will be reported. The Primary Safety analysis will be performed on the Safety Population.

14.8.4.2. *Analyses of Primary Effectiveness Endpoint*

- **Acute Procedural Success**: Acute success is defined as achieving confirmation of entrance block in all targeted PVs after adenosine and/ or isoproterenol challenge. The number and percentage of subjects who have reached acute success will be summarized. Primary Effectiveness analysis will be performed on the Effectiveness Population.

14.8.4.3. *Analyses of Secondary and Additional Endpoints*

No formal statistical hypotheses and inferential statistics will be formulated and performed for the secondary and additional endpoints. Details of analyses methods for secondary and additional endpoints will be provided in SAP.

Secondary Safety analysis for SADEs and AEs will be performed on the Safety Population. The neurological assessment related endpoints will be analyzed in the NAE population. Secondary Effectiveness (including Procedural Data) will be performed on the Effectiveness Population.

14.8.5. *Handling of Missing Data*

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

14.8.6. *Subgroup Analyses*

The results of the primary and secondary safety endpoints will be presented for the following subgroups:

- Sub-analysis on subjects where only TGA-mode was used for the procedure
- Sub-analysis on subjects where both TGA- and Q-mode were used for the procedure

The results of the primary and secondary effectiveness endpoints will be presented for the following subgroups.

- Sub-analysis on subjects where only TGA-mode was used for PVI
- Sub-analysis on subjects where both TGA- and Q-mode were used for PVI

15. Ethics and Protection of Human Subjects

15.1. Ethical Standard

As the Sponsor of this study, Biosense Webster has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration and the MDD 93/42/EC and the local government. The Sponsor will also maintain compliance with Good Clinical Practice (ICH version 4 du 1 May 1996), the European standard EN ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects), the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, Tokyo 2004), Sponsor general duties (21 CFR 812.40), selection of investigators (21 CFR 812.43), monitoring (21 CFR 812.46), supplemental applications (21 CFR 812.35 [a] and [b]), maintaining records (21 CFR 812.140 [b]), and submitting reports (21 CFR 812.150 [b)]), and to local regulations where required.

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

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

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

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

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

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

15.2. Informed Consent Process

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

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

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

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

The investigator and/or designee must also clearly document the process of obtaining informed consent in the subject's source documents. The voluntary process of obtaining informed consent confirms the subject's willingness to participate in the study. It's the investigator's responsibility to ensure that the informed consent process is performed in accordance with ICH-GCP and, where applicable, local and federal regulations. Subjects should not be coerced, persuaded, or unduly influenced to participate or continue to participate in the trial. Subjects or his/her legal representative must be given ample time and opportunity to inquire about details of the trial and all questions about the trial should be answered to the

satisfaction of the patient or the representative. Failure to provide written informed consent renders the subject ineligible for the study. If new information becomes available that can significantly affect a subject's future health and/or medical care, this information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing by dating and signing the amended ICF.

15.3. Participant and Data Confidentiality

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

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

15.3.1. *Research use of Stored Data*

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

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

16. Source Documents and Access to Source Data/Documents

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

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

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

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

17. Quality Assurance and Quality Control

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

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

The 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.

18. Data Handling and Record Keeping

18.1. Data Collection and Management Responsibility

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

18.1.1. *Data Collection*

Electronic Case Report Forms (eCRFs) will be used to collect all subject data during this clinical investigation. eCRFs have been developed to capture the information outlined in this clinical investigation plan. Modification to the eCRF will only be made if deemed necessary by the sponsor. Data on these eCRFs will be monitored (source verified) and the monitor will ask the site representative to correct if necessary to match the source documents. All changes made to the

data will be tracked in the electronic audit trail. The investigator will be required to sign designated eCRFs as verification that they have been reviewed and the data entered are correct. Data from these eCRFs will be used to provide analysis of this clinical investigation.

All CARTO® 3 v6 and Generator data files created during the procedure will be downloaded/ extracted and an anonymized copy provided to the sponsor for further evaluation.

18.1.2. *Data Reporting*

The investigator, or a designated individual, is responsible for ensuring that clinical investigation data are timely and properly recorded on each subject's eCRF and related documents. The investigator, or a designated individual, is required to electronically sign the eCRF on the appropriate pages to verify that he/she has reviewed and attests to the correctness of the recorded data. Completed eCRF will be reviewed and monitored by the sponsor personnel, or an appropriately qualified and trained designee, throughout the clinical investigation. To this end, the Investigator and institution must permit inspection of the trial files and subject eCRFs by such representatives and/or responsible government agencies.

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

Table 10 Responsibilities for Preparing and Submitting Reports

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

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

18.1.3. *Data Verification and Review*

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

18.1.4. *Final Data Analysis*

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

18.2. Study Record Retention and Archiving

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

If the investigator retires, relocates, or withdraws from assuming primary responsibility for keeping the study records, custody transfer per written notice must be submitted to the sponsor indicating the name and address of the person accepting primary responsibility. The EC must be notified in writing of the name and address of the new custodian. Record retention dates must be provided to all parties by the sponsor's corporation.

19. Study Suspension or Termination

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

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

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

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

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

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

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

20. Data and Publication Policy

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

All information concerning the study, 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.

21. Document Filing

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

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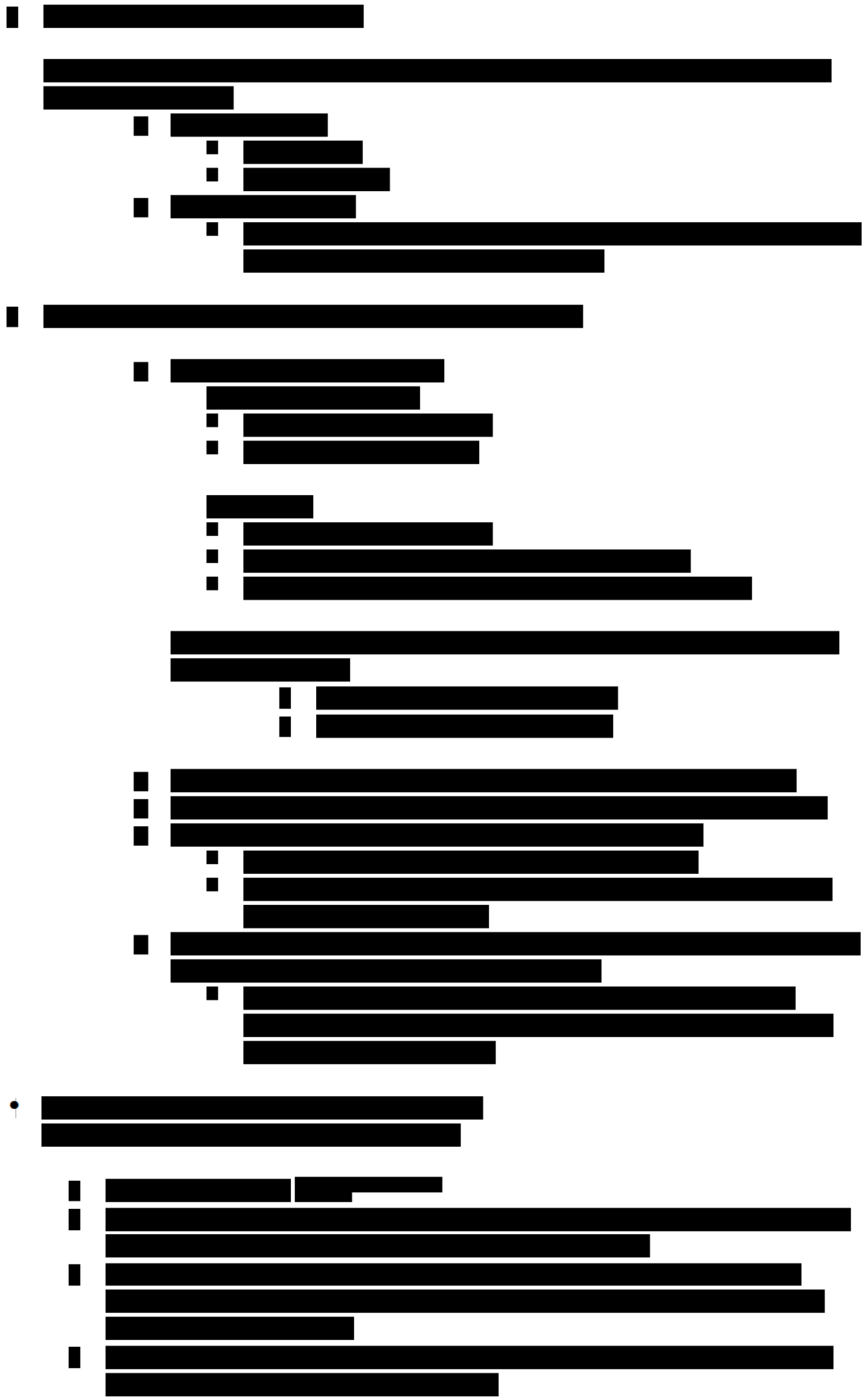

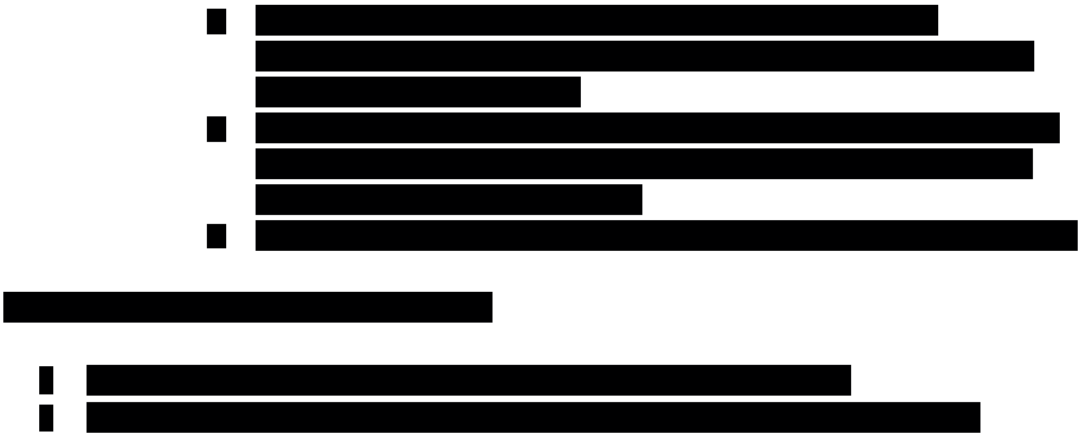

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