Safety and Effectiveness Evaluation of the THERMOCOOL SMARTTOUCH™ SF Catheter with the TRUPULSE™ Generator for treatment of drug refractory symptomatic Paroxysmal Atrial Fibrillation (PAF)

PulseSmart

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Sponsor: **BIOSENSE WEBSTER, INC.**
31 Technology Drive
Suite 200
Irvine, CA 92618
USA

History of Changes:



The Biosense Webster THERMOCOOL SMARTTOUCH™ SF Bi-Directional Navigation Catheter (D-1348-05-SI-10) and TRUPULSE™ Generator (D-1417-01-IC) system is for investigational device use only and is not commercially available anywhere in the world." THERMOCOOL SMARTTOUCH™ SF Bi-Directional Navigation Catheter and TRUPULSE™ Generator" are internal Biosense Webster project names and not intended for any other external use. The final commercial or trade name of the investigational system (THERMOCOOL SMARTTOUCH™ SF Bi-Directional Navigation Catheter and TRUPULSE™ Generator) may be different.

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2. List of Acronyms and Abbreviations

Acronym/ Abbreviation	Expanded Term
AAD	Antiarrhythmic Drug
ACC/AHA	American College of Cardiology/American Heart Association
ACE	Asymptomatic Cerebral Emboli
ACT	Activated Clotting Time
AE	Adverse Event
AEF	Atrio Esophageal Fistula
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect on Quality of Life
AFL	Atrial Flutter
AT	Atrial Tachycardia
CA	Competent Authority
CABG	Coronary Artery Bypass Graft
CEC	Clinical Events Committee
CF	Contact Force
CHF	Congestive Heart Failure
CIP	Clinical Investigation Plan
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatinine Phosphokinase
CRF	Case Report Form
CRO	Clinical Research Organization
CS	Coronary Sinus
CSR	Clinical Study Report
CT	Computed Tomography
CTI	Cavotricuspid Isthmus
CVA	Cerebrovascular Accident or Stroke
DD	Device Deficiency
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
EB	Ethics Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EHRA AF	European Heart Rhythm Association Atrial Fibrillation
EMEA	Europe, Middle East and Africa
EP	Electrophysiology
ESC	European Society of Cardiology

Acronym/ Abbreviation	Expanded Term
FAM	Fast Anatomical Mapping
FDA	Food and Drug Administration
Fr	French
FU	Follow-Up
GCP	Good Clinical Practices
GERD	Gastroesophageal Reflux Disease
HM	Holter Monitoring
HRS/EHRA/ECAS	Heart Rhythm Society / European Heart Rhythm Association / European Cardiac Arrhythmia Society
IB	Investigator Brochure
ICE	Intracardiac Echocardiography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instruction for Use
ILD	Interlesion Distance
IRE	Irreversible Electroporation
ITT	Intention to Treat
LA	Left Atrium
LBBB	Left Bundle Branch Block
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MDD	Medical Device Directive
MDR	Medical Device Regulation
MI	Myocardial Infarction
mITT	Modified Intent to Treat
MMSE	Mini Mental State Examination
MRA	Magnetic Resonance Angiogram
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NA	Neurological Assessment
NIHSS	National Institute of Health Stroke Scale
NYHA	New York Heart Association
PAF	Paroxysmal Atrial Fibrillation
PFA	Pulsed Field Ablation
PF energy	Pulsed Electric Field Energy
PI	Principal Investigator
PN	Phrenic Nerve
PNP	Phrenic Nerve Paralysis

Acronym/ Abbreviation	Expanded Term
PP	Per Protocol
PPI	Proton Pump Inhibitors
PsAF	Persistent Atrial Fibrillation
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
RF	Radiofrequency
RV	Right Ventricle
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOC	Standard Of Care
SP	Safety Population
SVC	Superior Vena Cava
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TS	Transseptal
TTE	Transthoracic Echocardiography
UADE	Unanticipated Adverse Device Effect
UM	User Manual
USADE	Unanticipated Serious Adverse Device Effect

3. Key Roles and Responsible Parties

SPONSOR:

Cardiovascular & Specialty Solutions (CSS)
Biosense Webster Inc.,
31 Technology Drive, Suite 200
Irvine, CA 92618 - USA
Tel: +1 800-729-9010

CONTACTS:

Director, Clinical Research, BWI, United States
PPD
31 Technology Drive, Suite 200
Irvine, CA 92618 - USA
PPD

Senior Director of Preclinical Research, Medical Affairs, BWI, United States
PPD
31 Technology Drive, Suite 200
Irvine, CA 92618 - USA
PPD

Clinical Research Manager, Australia
PPD
1-5 Khartoum Road
North Ryde, NSW 2113
PPD

CRO(S) AND CORE LAB(S):

The sponsor maintains a list of CRO(s) and Core Lab(s) and their contact information.

INVESTIGATORS:

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

4. Protocol Agreement and Statement of Compliance (Principal Investigator)

Study Title: Safety and Effectiveness Evaluation of THERMOCOOL SMARTTOUCH™ SF Catheter with the TRUPULSE™ generator for treatment of drug refractory symptomatic paroxysmal atrial fibrillation.
Study #: BWI202308

Principal Investigator:

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

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

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

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

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

_____

Principal Investigator Name [Print] **Date**

_____

Principal Investigator [Signature] **Site ID**

5. Protocol Synopsis

Full Title	Safety and Effectiveness Evaluation of THERMOCOOL SMARTTOUCH™ SF Catheter with the TRUPULSE™ Generator for treatment of drug refractory symptomatic Paroxysmal Atrial Fibrillation (PAF)
Short Title	PulseSmart
Protocol Number	BWI202308
Sponsor	Biosense Webster, Inc. 31 Technology Drive, Suite 200 Irvine, CA 92618 United States of America Tel: 1 800-729-9010
Indication	Drug refractory paroxysmal atrial fibrillation
Description of Study Devices	The Biosense Webster Pulsed Field (PF)/Radiofrequency (RF) Ablation System consists of the: • TRUPULSE™ Generator (D-1417-01-IC) • THERMOCOOL SMARTTOUCH™ SF Bi-directional Navigation Catheter (D-1348-05-SI-10) • CARTO™ 3 System V7.9 with PFA THERMOCOOL SMARTTOUCH™ SF Support (CARTO® 3 V7.9.1, CARTO® 3 V7.9 Phase 1) • Related components and accessories The Biosense Webster Ablation System provides a novel solution for the treatment of cardiac arrythmias by delivering pulsed field (PF) energy as an adjunct or alternative to radiofrequency (RF) energy to produce targeted intracardiac lesions and achieve the intended therapeutic effect. While currently approved RF systems rely on thermal energy to destroy (ablate) aberrant cardiac tissue, the PF technology ablates targeted cardiac tissue by application of ultrashort electrical pulses which induces cell membrane permeability resulting in irreversible electroporation (IRE). The principal components of the ablation system to be evaluated in this investigation are the THERMOCOOL SMARTTOUCH™SF Bi-Directional Navigation Catheter (also referred to as THERMOCOOL SMARTTOUCH™ SF (STSF) Catheter), the TRUPULSE™ Generator, and the CARTO™ 3 System V7.9.1 workstation. <u>TRUPULSE™ Generator (Investigational)</u> The TRUPULSE™ Generator is a specialized device that delivers radiofrequency (RF) and pulsed field (PF) energy through the study catheter. RF energy is delivered in power-controlled ablation mode at the selected power setting to a site in the heart via the study catheter.

PF energy consists of a series of short duration, high voltage, high-frequency, uni-polar, biphasic pulses (or “trains” of pulses) being applied to a site in the heart via the study catheter. The generator delivers PF energy in predefined voltage, pulse length, and number of pulses which have been optimized in pre-clinical testing to target cardiac tissue and produce durable lesions.

The generator is compatible with the Biosense Webster CARTO™ 3 System, nGEN™ Pump and standard electrophysiology (EP) lab equipment.

The TRUPULSE™ Generator is indicated for use in conjunction with compatible cardiac ablation catheters to deliver RF or PF energy during cardiac ablation procedures.

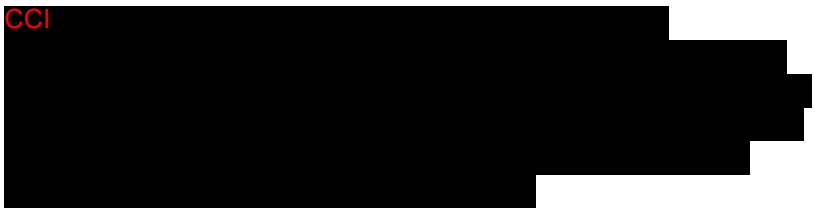
<u>THERMOCOOL SMARTTOUCH™ SF Bi-Directional Navigation Catheter (Investigational)</u>

The THERMOCOOL SMARTTOUCH™ SF (STSF) Bi-Directional Navigation Catheter (also referred to THERMOCOOL SMARTTOUCH™ SF (STSF) Catheter) with Contact Force Sensing Capability, is a steerable, multi-electrode luminal, irrigated catheter. The STSF Catheter is registered for use in catheter-based cardiac electrophysiological mapping (stimulating and recording) and, when used with a compatible generator, for cardiac ablation. The catheter has a high-torque shaft, with a bi-directional deflectable tip section, containing an array of electrodes which includes a 3.5 mm tip dome.

All electrodes may be used for recording and stimulation purposes. The tip electrode serves to deliver energy to the desired ablation site. The catheter incorporates a thermocouple temperature sensor that is embedded in the tip electrode. The high torque shaft allows the plane of the curved tip to be rotated to facilitate accurate positioning of the catheter tip at the desired site. The STSF Catheter provides a real time measurement of contact force between the catheter tip and heart wall, as well as location information when used with the CARTO™ 3 System.

The STSF catheter is to be used in this investigational study with the TRUPULSE™ Generator, to transmit the PF or RF energy to the catheter tip electrode for cardiac ablation.

CCI



Premarket or Post market	Premarket
Study Design	This is a prospective, single arm, multi-center, clinical evaluation of the Biosense Webster Ablation System to demonstrate safety and effectiveness of the system for the treatment of Paroxysmal Atrial Fibrillation (PAF) comparing to corresponding performance goals. The study will enroll 135 subjects with drug refractory PAF who are candidates for atrial fibrillation ablation. All subjects will be followed for 12 months and scheduled for evaluation at 7 days, 1-, 3-, 6- and 12-month following index ablation procedure. CCI [redacted] The study will declare early success if both primary safety and primary effectiveness endpoints are met at the early success interim analysis.
Sample Size	135 subjects will be enrolled in the study.
Study Population	Subjects undergoing catheter ablation for the treatment of drug refractory symptomatic PAF.
Geographic areas to be included	Approximately 10 sites in Canada and Australia
Anticipated Study Timeline	Estimated 17-19 months total study duration: – Enrollment: Approximately 5-7 months – Primary endpoint evaluation: 12 months post procedure
Procedure(s) description	Subjects will arrive at the electrophysiology (EP) 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 the below sequence: 1. Anatomical mapping of the LA 2. Pulmonary Vein Isolation (PVI) using the investigational ablation system 3. Confirmation of PV isolation (entrance block) with adenosine/isoproterenol challenge 4. If necessary, treatment of acute reconnections with additional applications of PF/RF energy 5. Confirmation of entrance block of all targeted PVs at the end of procedure In this study protocol, PF energy with the STSF Catheter is to be used for achieving PVI at the posterior and inferior segments of the PVs. RF energy is to be used for the anterior, roof, ridge and carina regions. In

<table>
<tr><td></td><td>CCI [redacted]

All subjects will undergo PVI with the Biosense Webster Ablation System until PVI is achieved and isolation is confirmed. CCI [redacted]</td></tr>
<tr><td>Primary Objective</td><td>The primary objective of this clinical investigation is to demonstrate safety and effectiveness of the BWI Ablation System when used for isolation of the atrial PVs in treatment of subjects with PAF. Specifically:
To demonstrate the safety based on early-onset (within 7 days of ablation procedure) primary adverse events
To demonstrate 12-month effectiveness off AAD based on freedom from documented symptomatic and asymptomatic atrial arrhythmia (atrial fibrillation (AF), atrial tachycardia (AT) or atrial flutter (AFL) episodes during the effectiveness evaluation period (Day 91-365)</td></tr>
<tr><td>Secondary objective</td><td>The secondary objective of this clinical investigation is to evaluate Quality of Life (QOL) up to 12 months.</td></tr>
<tr><td>Additional objectives</td><td>The additional objectives of this study are to evaluate acute procedure success, procedural data, the incidence of (procedure and/or device related) serious adverse events during and after procedure up to 12 months.</td></tr>
<tr><td>Primary Endpoints</td><td>Acute Safety
The primary safety endpoint is the occurrence of early onset Primary Adverse Events (PAE) within seven (7) days of an ablation procedure (including the initial and repeat procedures), using the BWI Ablation System per protocol.
PAEs include the following Adverse Events (AEs)
<table>
<tr><td>Esophageal perforating complications (Atrio-Esophageal Fistula[1], esophago-pericardial fistula)</td><td>Phrenic Nerve Paralysis (permanent)[5]</td></tr>
<tr><td>Cardiac Tamponade[2, 3]/perforation[2]</td><td>Pulmonary Vein Stenosis[6]</td></tr>
<tr><td>Device or procedure related death[4]</td><td>Stroke/CVA[7, 8]</td></tr>
<tr><td>Major Vascular Access Complication/Bleeding</td><td>Thromboembolism</td></tr>
<tr><td>Myocardial Infarction</td><td>Transient Ischemic Attack (TIA)</td></tr>
<tr><td>Pericarditis</td><td>Heart Block</td></tr>
<tr><td>Pulmonary Edema (Respiratory Insufficiency)</td><td>Vagal Nerve Injury/Gastroparesis[9]</td></tr>
</table>
[1]Atrio-esophageal fistula occurring up to 90 days post AF ablation process procedure will be considered a PAE.
[2]Cardiac Tamponade/Perforation occurring up to 30 days post AF ablation process procedure will be considered a PAE.
[3] Hemodynamic compromise or instability is defined as Systolic BP < 80 mm Hg.</td></tr>
</table>

[4]Device or procedure-related death anytime during or after the ablation procedure and any death reported within 30 days of ablation procedure where device and/or procedure relatedness cannot be determined via CEC adjudication.
[5] Absent phrenic nerve function as assessed by a sniff test.
[6] Pulmonary Vein Stenosis occurring anytime during the 12 month follow up period will be considered a PAE.
[7] Non-focal global encephalopathy requires unequivocal evidence based upon neuroimaging studies to be reported as a stroke
[8] Modified Rankin score assessments should be made by certified individuals.
[9] Vagal nerve injury is considered to be a major complication if it requires or prolongs hospitalization, or results in ongoing symptoms for more than 30 days following an ablation procedure.

Primary Effectiveness

The primary effectiveness endpoint is achieving freedom from documented (symptomatic and asymptomatic) atrial tachyarrhythmia (AF, AT or AFL of unknown origin+) episodes based on electrocardiographic data (12-lead ECG or ≥30 seconds on ECG or sponsor provided Holter device) during the effectiveness evaluation period (Day 91-Day 365), and freedom from the following failure modes:

- Acute procedural failure, including:
  - Failure to achieve entrance block in all pulmonary veins using the investigational device (except those that are silent and/or cannot be cannulated post-procedure) by the end of the procedure.

- Repeat ablation failure, including:
  - More than 1 repeat ablation procedure for AF/AT/ AFL (of unknown origin[+]) during the 3-Month Blanking Period (Day 0-90 post index procedure).
  - Any repeat ablation procedure for AF/AT/ AFL (of unknown origin[+]) during the evaluation period.

- Non-study device failure, including:
  - Use of a non-study device to treat PV targets to achieve isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) during index or repeat procedure in the blanking period.
  - Use of a non-study device for ablation in the left atrium during either index or repeat procedure within the blanking period.

- AAD failure:
  - Taking a new AAD (Class I & III) for atrial tachyarrhythmia (AF, AT or AFL of unknown origin[+]) or taking a previously failed Class I/III AAD after the 3-month follow-up visit window (i.e., any time beyond Day 104 to 365 post index procedure).
  - Oral amiodarone is prescribed/taken post index ablation procedure.

	• Continuous AF/AT/AFL of unknown origin+ on a standard 12-lead ECG during the effectiveness evaluation period. • Any DC cardioversion procedure during the evaluation period for documented atrial tachyarrhythmia (AF, AT or AFL of unknown origin+) recurrences ascertained through protocol specified arrhythmia monitoring methods (12-lead ECG, Holter). C [redacted] C
Secondary Endpoint	QOL Improvement: Atrial Fibrillation Effect on Quality-of-Life (AFEQT) Questionnaire will be used to assess the quality-of-life post ablation procedure. The endpoint is the change in quality of life, as measured by the total AFEQT score, at 12-month post procedure, in comparison to baseline assessment.
Additional Effectiveness Endpoints	The following additional effectiveness endpoints will be assessed: • Acute procedural success: the achievement of electrical isolation for all PVs which is evidenced by the confirmation of entrance block at the end of the procedure. Use of solely RF mode for PV isolation, resulting from study device malfunction leading to a failure in PF energy delivery is also deemed a failure. • Acute reconnection: the restoration of electrical conduction in the targeted veins, which is identified by adenosine/isoproterenol challenge. • First pass isolation: the achievement of entrance block in targeted veins after the first encirclement, which is evaluated prior to the adenosine challenge. • Ablation by a non-study device for PVI touch-up: Use of non-study device for touch-up ablation to achieve PV isolation in all clinically relevant targeted PVs. • Repeat ablation procedures for left atrial arrhythmia (AF, AT or AFL of unknown origin*) within the 12-month FU period will be assessed. The evaluation will include the timing of repeat ablation (blanking period or after blanking), any reconnections of targeted PVs from the index procedure, and the type of arrhythmia treated during the repeat ablation, along with their corresponding targets. • 12 Month Single Procedure Treatment Success: freedom from documented symptomatic atrial tachyarrhythmia (AF, AT or AFL of unknown origin+) episodes based on electrocardiographic data (12-lead ECG or ≥30 seconds on ECG or sponsor provided Holter

	device) during the effectiveness evaluation period (Day 91-Day 365) following a single index ablation procedure, and freedom from the following failure modes: ○ Acute procedural failure: Failure to achieve entrance block in all pulmonary veins using the investigational device (except those that are silent and/or cannot be cannulated post-procedure) by the end of the procedure. ○ Non-study device failure: use of a non-study device to treat pulmonary vein targets to achieve isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) during the index procedure. ○ Any repeat ablation procedure for AF/AT/ AFL (of unknown origin+) post the index procedure. • 12-Month freedom from symptomatic recurrence (Clinical Success): freedom from documented symptomatic atrial tachyarrhythmia (AF, AT or AFL of unknown origin+) episodes based on electrocardiographic data (12-lead ECG or ≥30 seconds on ECG or sponsor provided Holter device) during the effectiveness evaluation period (Day 91-Day 365). • Hospitalization for cardiovascular events: the impact of ablation procedure on CV hospitalization 12M after the index procedure, in comparison to the hospitalization history 12M prior to enrollment. • DC Cardioversion: the impact of ablation procedure on the number of receiving DCCV 12M after the index procedure, in comparison to the 12M history of DCCV prior to enrollment. • AAD Utilization: utilization of Class I/III antiarrhythmic drugs during the follow-up, in comparison to the baseline AAD use. [redacted]
Additional Safety Endpoints	**Safety** • Occurrence of Serious Adverse Device Effects (SADEs) • Occurrence of Unanticipated (Serious) Adverse Device Effect (UADEs and USADEs) • Occurrence of non-serious adverse events (non-SAEs) • Occurrence of device and/or procedure related Serious Adverse Events (SAEs) within 7 days (early-onset), 8 to 30 days (peri-procedural) and >30 days (late onset) of initial ablation procedure

Additional Procedural Endpoints	**Procedural data, including but not limited to:** • Total procedure time (from first femoral puncture to last catheter out) • PVI time • PF/RF application time • Mapping time • Number of PFA/RF applications at left and right PV • Total fluoroscopy time • Fluid delivered from the study catheter • Total study catheter left atrial dwell time • Ablation parameters per application ((e.g., temperature, power, impedance, contact force (CF), PF or RF, RF power, contact force, PF/RF tag index per segments etc.) • VISITAG SURPOINT™ values (Tag Index) per segment • Power Range • CF Range • Use of paralytics and type of anesthesia • Device Deficiency Information (if applicable)
Sample Size	**Total Sample size:** The total sample size of 135 is determined through trial simulations and is selected for providing desirable operating characteristics. CCI [redacted] CCI [redacted] CCI [redacted] Based on a performance goal (PG) of 12% for the primary safety endpoint and a PG of 50% for the primary effectiveness endpoint, CCI [redacted] simulation results demonstrated that a sample size of 135 subjects will provide CCI [redacted] to declare success for both endpoints under the alternative hypotheses, while controlling the overall type-I error rate at one-sided 2.5%. CCI [redacted] for the primary safety and effectiveness endpoints, respectively.
Inclusion Criteria	1. Diagnosed with Symptomatic PAF (Physician's note indicating recurrent self-terminating AF). At least one (1) electrocardiographically documented AF episode within twelve (12) months prior to enrollment. Electrocardiographic documentation may include, but is not limited to,

	electrocardiogram (ECG), Holter monitor, or other electrocardiographical devices accepted by investigators. 2. Failed at least one (1) Class I or Class III AAD as evidenced by recurrent symptomatic AF or has intolerable side effects or is contraindicated to the Class I or Class III AAD. 3. Age 18 - 80 years. 4. Able and willing to comply with all pre-procedure, post-procedure, and follow-up testing and visit requirements. 5. Willing and capable of providing consent.
Exclusion Criteria	1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause (e.g., documented obstructive sleep apnea, acute alcohol toxicity, morbid obesity (Body Mass Index >40 kg/m^2), renal insufficiency (with an estimated creatinine clearance < 30 mL/min/1.73 m^2) ….). 2. Previous LA ablation or surgery 3. Patients known to require ablation outside the PV region (atrioventricular reentrant tachycardia, atrioventricular nodal reentry tachycardia, atrial tachycardia, atrial flutter of unknown origin, ventricular tachycardia and Wolff-Parkinson-White). 4. Previously diagnosed with persistent AF (> 7 days in duration) 5. Severe dilatation of the LA (documented LAD >50mm antero-posterior diameter on imaging within 6 months prior to enrollment 6. Documented left atrium (LA) thrombus within 48 hours prior to the index procedure by TEE, or by ICE prior to transeptal puncture during procedure. 7. Documented severely compromised LVEF (LVEF <40%) by imaging within 6 months prior to enrollment 8. Uncontrolled heart failure or New York Heart Association (NYHA) Class III or IV 9. History of blood clotting, bleeding abnormalities or contraindication to anticoagulation (heparin, warfarin, or dabigatran) 10. History of a documented thromboembolic event (including TIA) within the past 12 months, or history of a documented left atrial appendage (LAA) thrombus 11. History of a documented symptomatic lacunar infarction within the past 12 months 12. Previous PCI/MI within the past 2 months 13. Coronary Artery Bypass Grafting (CABG) surgery within past 6 months 14. Valvular surgery, cardiac surgery (e.g., ventriculotomy, atriotomy) or valvular cardiac (surgical or percutaneous) procedure. 15. Unstable angina pectoris within the past 6 months 16. Anticipated cardiac transplantation, cardiac surgery or other major surgery within the next 12 months. 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 severe chronic symptoms 18. Known significant PV anomaly that in the opinion of the investigator

	would preclude enrollment in this study 19. Has known pulmonary vein stenosis 20. Pre-existing hemi diaphragmatic paralysis 21. Acute illness, active systemic infection or sepsis 22. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes catheter introduction or manipulation. 23. Severe mitral regurgitation (Regurgitant volume 60 mL/beat, Regurgitant fraction 50%, and/or Effective regurgitant orifice area 0.40cm2) 24. Presence of implanted pacemaker, Implantable Cardioverter-Defibrillator (ICD), recently implanted (within 6 months) LAAO device or other implanted metal cardiac device within the cardiac space that may interfere with the energy field created during the ablation procedure. 25. Presence of a condition that precludes vascular access (such as IVC filter) 26. Significant congenital anomaly or a medical problem that in the opinion of the investigator would preclude enrollment in this study 27. Categorized as vulnerable population and requires special treatment with respect to safeguards of well-being 28. Current enrollment in an investigational study evaluating another device or drug. 29. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of childbearing age and plan on becoming pregnant during the course of the clinical investigation. 30. Life expectancy less than 12 months 31. History of massive haemorrhage within the past 6 months. 32. Presenting contra-indications for the devices
Statistical Analysis	**Primary Endpoints and Associated Hypothesis** **Primary Safety Endpoint Analysis:** The formal hypotheses for testing the primary safety endpoint are given as follows: H_0: $P_S \geq 0.12$ H_a: $P_S < 0.12$ where P_S represents the primary adverse event rate. **Primary Effectiveness Endpoint Analysis:** The formal hypotheses for testing the primary effectiveness endpoint are given as follows: H_0: $P_E \leq 0.5$ H_a: $P_E > 0.5$ where P_E represents the 12-month effectiveness success rate. **<u>Early Success Interim Analysis</u>**

CCI

	Secondary Effectiveness Endpoint Analysis: The formal hypotheses for testing the secondary endpoint of quality-of-life improvement are given as follows: $H0: \mu_d \leq 0$ vs. $HA: \mu_d > 0$, where μ_d is the mean change of overall AFEQT scores between baseline AFEQT score and 12-month AFEQT score (i.e., $AFEQT_{12M} - AFEQT_{baseline}$). CCI [redacted]
CCI [redacted]	[redacted]
Independent Committees/ Reviewers	DMC and CEC will be established for this study • DMC will assess clinical safety data on regular intervals and make recommendations on study adaptations. • CEC will adjudicate primary safety endpoint events. • The early success interim analysis will be conducted by an independent biostatistician. The result of the analyses will be presented to the DMC by the independent biostatistician. The Sponsor (i.e., BWI) will not be informed of the results until the DMC provides a recommendation for early trial success, upon which the preparation of the early success interim analysis report will commence accordingly.
Time and Events Schedule	**See Table 1 below**

Table 1: Subject Treatment and Follow-up Schedule

	Pre-Procedure	Ablation/ Discharge		Phone/ Virtual	Follow-Up Visits				
	Screening / Baseline	Study Abl[1] Day 0	D/C	7 D D7-10	1 M D23-37	3 M D76-104	6M D150-210	12M D335-395	UNS
Visit no.	1	2	3	4	5	6	7	8	90
Informed consent[1]	X								
Inc & Excl Criteria	X								
Demographics	X								
Vital Signs	X								
Physical Exam	X		X		X	X	X	X	X
Med History[2]	X			X^2	X^2	X^2	X^2	X^2	X^2
Hospitalization/ CV history	X								
AF History	X								
12-Lead ECG	X^3		X		X^3	X	X	X	X^3
Adverse Events[4,5]	X	X	X	X	X	X	X	X	X
CHA_2DS_2-VASc and $CHADS_2$ Score	X								
NYHA Scale	X								
QOL Assessment[6]	X					X	X	X	
Pregnancy Test[7]	X								
LA size and LVEF imaging[8]	X								
LA Thrombus Imaging[9]	X								
Ablation Assessments		X							
Device Deficiency		X							
TTE[10]			X						
Concomitant Medications[11]	X	X	X	X	X	X	X	X	X
Repeat Ablation[12]				X	X	X	X	X	X
AF/AT/AFL recurrence			X	X	X	X	X	X	X
24 Hr Holter[13]						X	X	X	
Completion/ discontinuation form[14]		X	X	X	X	X	X	X	

1 Initial ablation procedure should be done within 90 days of consent.

2 Medical history including but not limited to arrhythmia, AAD therapy, and thromboembolic events. In subsequent visits, medical history is collected to confirm no changes in medical history since last visit.

3 Data from 12-lead ECG recordings will be collected, if available. For pre-procedure, can be performed before ICF signature.

4 AEs collected once consent has been signed. Collected to confirm no changes in health status since last visit.

5 If AE results in hospitalization, data should be collected.

6 Quality of life tools (AFEQT).

7 Pregnancy test must be done on pre-menopausal women only, within 24 hours of the procedure.

8 Imaging within 6 months prior to procedure to assess the LA and LVEF. In case the imaging assessment is older than 6 months, LA/LVEF dimensions shall be re-measured during the index procedure prior to insertion of the study catheter.

9 Subjects must undergo imaging (using one of the following modalities TEE or ICE) to rule out the presence of LA thrombus within 48 hours of the ablation procedure.

10 All subjects will undergo TTE prior to discharge to evaluate pericardial effusion.

11 Concomitant medication: only cardiac (i.e., anti-arrhythmia drugs, anticoagulation regimen, etc.) & index procedure related (i.e., adenosine, anticoagulation, pain medication)

12 Information on any repeat ablation after the index procedure will be collected.

13 Arrhythmia monitoring via 24H Holter, site to contact subject and verify if any symptoms experienced during the Holter monitoring.

14 12-month visit/last completed visit or last data collection

6. Background Information and Scientific Rationale

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 to approximately 8% in patients over 80 years of age.[1, 2] The primary clinical benefit of AF ablation is improvement in Quality of Life (QoL) resulting from the elimination of arrhythmia-related symptoms such as palpitations, fatigue, or effort intolerance. In recognition of this, the elimination of symptomatic atrial arrhythmias was recommended by the 2017 HRS/EHRA/ECAS Consensus on Catheter and Surgical Ablation of Atrial Fibrillation.[3]. The opinion of the ESC as expressed in their 2020 AF Management Guidelines is that "Catheter ablation of symptomatic Paroxysmal Atrial Fibrillation (PAF) is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on Antiarrhythmic Drug (AAD) therapy and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced center."[1, 4, 5]

The 2017 HRS/EHRA/ECAS consensus statement states that electrical isolation of the Pulmonary Veins (PVs) from the Left Atrium (LA) is the "cornerstone for most AF ablation procedures" and that "complete electrical isolation of all PVs should be the goal."[3] Point-by-point ablation with radiofrequency (RF) catheters has provided positive results for treating many types of supraventricular arrhythmias[6, 7], including PAF.[6-12]

The Biosense Webster ThermoCool® SmartTouch® catheters provide real-time measurement of contact force (CF) between the catheter tip and heart wall, as well as location information, when used with CARTO™ 3 Navigation System and have been associated with increased acute and long-term procedural success in the paroxysmal AF population. Multiple studies have shown CF-guided ablation protocol aiming to enclose the veins with stable, contiguous and optimized RF lesions is associated with a high incidence of successful PVI, high single-procedure arrhythmia-free survival at 1 year, marked reduction in arrhythmia burden, and a high likelihood of finding four isolated veins at repeat ablation.[13, 14]

Most of the catheter ablation systems are thermal energy-based and use either heat or cold energy to destroy arrhythmogenic tissues. The ablation has been connected with arrhythmia recurrences due to incomplete lesion creation. It is also associated with severe complications such as pulmonary vein (PV) stenosis, phrenic nerve damage, coronary artery damage, atrioesophageal fistula, steam pop and ensuing cardiac perforation and pericardial tamponade.[3, 15, 16]

In the past decades, extensive research into alternative energy forms for ablation has been conducted to improve ablation efficiencies and reduce ablation-related complications. One of the new technologies for lesion creation is based on electroporation by pulsed field (PF) ablation. Electroporation is a process in which an electric field is applied to the cell/tissue for a short period of time that results in pore formation in the cell membrane and a subsequent increase in cell permeability.[17] The electric field strength and duration could cause reversible or irreversible permeabilizations.[18] At low electric field strength and a short duration, the cell membrane forms nanosized pores, allowing small or medium sized molecules, such as drug and DNA, flow across the lipid bilayer. The pore formation is transient and reversible. The affected cells are able to survive from this reversible electroporation. At medium electric field strengths, the density of pore formation in the membrane increases to a certain level such that the process becomes irreversible. Free flows of water and ions in and out of the cell membrane result in the loss of cellular homeostasis, ultimately triggering the apoptosis and cell death.

This irreversible aspect of the process is thus called “irreversible electroporation” or IRE.[15, 17] Finally, at high electric field strengths, the cell membrane quickly undergoes fragmentation resulting in necrotic cell death.[17]

The PF system generally consists of electric field generator and electric current applicators. The electric field required for IRE could be delivered by applying a high voltage or direct current (DC) across electrodes in contact with cardiac tissues.[17] Different kinds of electric currents, such as DC, alternate current (AC), pulsed DC, or a combination of these were used to generate the electric field for IRE in preclinical and clinical studies.[19] Pulsed DC was the most commonly used energy source in preclinical and clinical studies.[20, 21] Early studies found that the strength of the electric field delivered by pulsed DC is dictated by pulse shape, pulse duration, pulse height, pulse polarity, pulse interval, number of pulses per application or pulse train, number of pulse trains delivered, and interval between pulse train deliveries.[17, 18, 22]

Influence on adjacent structures has been previously studied. Of the well described complications in RF ablation techniques, the tissue specificity of IRE has been considered as a major advantage.[23] The IRE effect on the phrenic nerve has been described to be recoverable, suggesting that permanent damage can be avoided with IRE.[24-27] A rare but dangerous complication of RF ablation, namely development of lethal Atrio-Esophageal Fistula (AEF), might be minimized with IRE as it’s suggestive that the risk with IRE would only be limited to the muscular layer of the esophagus.[28]

A previous study with lattice-tip catheter using combined RF/PF ablation showed the benefit of using PFA on atrial myocardium without damage to adjacent structures.[29] In addition, the use of a focal PFA catheter was published to treat CTI and linear ablations in PAF and PsAF patients. Lesions were found to be durable.[30, 31] No safety concerns were outed[29]. However, transient coronary spasm was reported as a possible consequence of ablation of mitral isthmus line.[32, 33]

6.1 Previous Experience with the STSF Catheter and TRUPULSE™ Generator

6.1.1 Pre-Clinical Experience with the STSF Catheter and TRUPULSE™ Generator

Bench and animal testing were performed using the THERMOCOOL SMARTTOUCH™ SF Bi-Directional Catheter and TRUPULSE™ generator. A robust program of pre-clinical testing was completed to demonstrate safety and effectiveness when using the STSF catheter with the TRUPULSE™ Generator to create lesions using either of the two energy modes. An in vivo simulated clinical procedure (porcine beating heart model) was performed by five physician evaluators and included their evaluation of overall system performance. The preclinical evidence also established equivalence of the TRUPULSE™ Generator when delivering RF energy via the STSF Catheter to a commercially available RF Generator. In addition to demonstrating equivalence in a simulated clinical procedure, lesion equivalence is further demonstrated via side-by-side thigh prep model to the nGEN™ Generator. The animal testing validates the use of the STSF Catheter and TRUPULSE™ Generator at the targeted ablation locations and met the acceptance criteria of safety and efficacy assessment.

The utilization of Ablation index study demonstrates that there is a linear correlation between PF Index (derived from contact force and number of applications) and lesion dimension sufficient to predict accuracy within ±2 mm. The results of this study compliment recommendations already in place for VISITAG™ Surpoint for RF and our guidelines will remain unchanged for this prospective tool during PVI. For Anterior targets the user may use an Index target of 380 and for posterior targets a value of 550 are recommended.

6.1.2 Previous Clinical Evaluations with STSF catheter (D-1348-XX-S)

The THERMOCOOL SMARTTOUCH™ SF Bi-Directional Catheters (D-1348-XX-S) were placed on the EU market under Medical Device Directive (93/42/EEC) on January 7, 2011. The catheter received CE mark authorization under Medical Device Regulation (2017/745) on July 27, 2022. Since CE mark certification additional data has been published on the STSF catheters via post-market clinical follow-up studies. The SMART-SF[34, 35], PRECEPT[36], VISTAX[13] and SURPOINT[37] study provided supportive evidence on the safety and performance of the THERMOCOOL SMARTTOUCH™ SF catheter over defined device lifetime. In Canada, the THERMOCOOL SMARTTOUCH™ SF Bi-Directional Catheters (D-1348-XX-S) were first licensed on January 20, 2015 (License 89000). The clinical literature data supports the safety and performance of the THERMOCOOL SMARTTOUCH™ SF catheters when used as intended to facilitate electrophysiological mapping of the heart and to transmit RF energy to the catheter tip electrode for ablation purposes.

6.1.3 Previous Clinical Evaluations with a similar Generator

Pulse Field Ablation (PFA) System for the Treatment of Paroxysmal Atrial Fibrillation (PAF) by Irreversible Electroporation (IRE), the InspIRE clinical study (BWI2019_08)

The 'inspIRE' clinical study (NTC04524364) is a pre-market, prospective, multicenter, single arm clinical evaluation utilizing the BWI Circular IRE Catheter and Multi-Channel IRE Generator. The objective of the study is to demonstrate safety and long-term effectiveness of the IRE system (Circular IRE Catheter and IRE Generator) in the isolation of the atrial pulmonary veins in treatment of subjects with PAF.

The inspIRE study consists of two sequential waves; WAVE I, the safety characterization phase, with intention to delineate safety and provide preliminary estimates for safety and acute effectiveness of the IRE system, enrolled 45 subjects between August 2020 and April 2021.

Purpose of the WAVE II phase was to evaluate safety and long-term effectiveness. Sample size of WAVE II was determined based on accruing data and a successful interim analysis was performed in May 2022. A total of 227 subjects were enrolled between March 2021 and May 2022 and currently subjects are still in follow-up.

Acute procedural success, defined as confirmation of entrance block in all clinically relevant targeted pulmonary veins after adenosine/isoproterenol challenge without use of a non-study catheter to achieve PVI, was achieved in all subjects treated with the study catheter in WAVE I of the study.

No primary adverse events including, atrio-esophageal fistula, phrenic nerve paralysis, cardiac tamponade/perforation, pulmonary vein stenosis, device or procedure- related death, or stroke/CVA have been reported in the WAVE I phase of the study.

Assessment of Safety and Effectiveness in Treatment Management of Atrial Fibrillation with the BWI IRE Ablation System, the admIRE clinical study (BW2019_10)

The 'AdmIRE' clinical study (NCT05293639) is a prospective, non-randomized, multi-center, clinical evaluation of the BWI IRE Ablation System to demonstrate safety and long-term effectiveness for the treatment of drug refractory symptomatic paroxysmal atrial fibrillation. This study is conducted in the United States. The BWI IRE Ablation System consists of the VARIPULSE™ Bi-Directional catheter

and TRUPULSE™ Generator. Enrollment commenced on 20th April 2022 in the United States and was completed on 15th November 2022.

A summary of previous clinical investigations with similar devices are listed in Appendix 2.

Safety and Effectiveness Evaluation of the THERMOCOOL SMARTTOUCH™ SF Catheter with the TRUPULSE™ Generator for Treatment of Paroxysmal Atrial Fibrillation (PAF)

The 'SmartfIRE' clinical study is a prospective, single arm, multi-center, clinical evaluation of the BWI PF/RF Ablation System, the THERMOCOOL SMARTTOUCH™ SF (STSF) Catheter in conjunction with the TRUPULSE™ Generator and Carto software incorporating PF/RF ablation index, to demonstrate safety and effectiveness of the system for the treatment of Paroxysmal Atrial Fibrillation (PAF) comparing to corresponding performance goals. The study is being conducted in Europe with first patient enrolled on February 27th, 2023.

Safety and Effectiveness Evaluation of the THERMOCOOL SMARTTOUCH™ SF Catheter with the TRUPULSE™ Generator for Treatment of Paroxysmal Atrial Fibrillation (PAF)

The 'SmartPulse PAF' clinical study is a prospective, single arm, multi-center, clinical evaluation of the Biosense Webster Ablation System to demonstrate safety and effectiveness of the system for the treatment of Paroxysmal Atrial Fibrillation (PAF) comparing to corresponding performance goals. The study is currently planned to be conducted in the United States. Enrollment has not started.

6.2 Potential Risk and Benefit

The overall risks posed by use of the STSF Catheter, with the TRUPULSE™ Generator are expected to be comparable to those anticipated during routine use of radio frequency (RF) catheter ablation systems and use of AAD therapy according to current AF management guidelines. Appropriate measures have been outlined in this protocol to minimize the risk to subjects, while still providing the possible benefits (including but not limited to safety/effectiveness) of the treatment options to be studied.

Pulse-field ablation used to create irreversible electroporation has been used in the treatment of oncology for the past decade, although treatment of patients with Atrial Fibrillation with this technology began only recently. Nonetheless, when compared to the usual standards of practice and published literature few, if any, the occurrence of thermal injuries which can be caused by RF ablation, are minimized with pulse field ablation.

The STSF Catheter IFU and TRUPULSE™ User Manual warn users of all potential risks associated with the use of RF and PF energy. Refer to the IFU and UM for a complete list of contraindications, warning, and precautions of both devices.

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

6.2.1 Known Potential Risks

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

Pericarditis: According to HRS guidelines, 2017, pericarditis incidence is varying from 0%-50% as a complication to AF ablation. Pericarditis can occur due to mechanical or thermal irritation of the myocardium. This tends to be underreported as it is usually transient and resolves without invasive intervention.[38] The risk for pericarditis will be further minimized by the use of PF energy, which is minimal thermal.

Phrenic Nerve Palsy (PNP): Although injury to the Phrenic Nerve (PN) is rare for RF (<1%) and not expected with the PF energy provided, stimulation of the phrenic nerve that resolves acutely has been noted in the literature.[24] Prior to ablation in the region of the RSPV, investigators are encouraged to perform precautionary measures such as evaluation of proximity to the phrenic nerve and pacing maneuvers.[38] Additionally, no new ablations should be delivered on or near the PN if evidence of PN impairment is observed and the catheter should be repositioned.

Atrio-Esophageal Fistula (AEF): AEF is a rare (0.02%-0.11%) but catastrophic complication of AF ablation that can occur due to the anatomical proximity of the esophagus to the posterior wall of the LA and that is associated with a high mortality rate.[39] In patients, the application of traditional RF energy along the posterior LA can result in thermal injury to the esophagus and the formation of an AEF.[38] As PF energy is non-thermal, AEF is not an expected outcome and has not been reported in the literature to date.[28,40] Per CIP , PF energy is recommended on the posterior wall. Many investigators attempt to mitigate esophageal damage by monitoring endoluminal temperature during the ablation procedure.

Pulmonary vein stenosis: Pulmonary vein stenosis (PVS) is a well-known complication of thermal catheter ablation of atrial fibrillation. In RF procedures, the risk of PV stenosis is small (<1%)[41]. The risk of pulmonary stenosis associated with a pulsed field energy ablation procedure is expected to be unlikely and to date has not been reported following pulsed field applications. PVS can be prevented by delivering energy outside the pulmonary vein ostium and by using a wide circumferential technique.

Thrombus formation: The incidence of thromboembolism associated with AF ablation is reported to be between 0% and 7%[41]. Thrombus generated during the ablation procedure may pose a serious and even life-threatening risk to the patient. Embolization of thrombus could produce 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. Thrombus could form due to temperature / impedance rise at the catheter-tissue region, insufficient level of anti-coagulation or lack of irrigation. The study catheter is irrigated and irrigation settings per the catheter's Instructions for Use should be maintained throughout the procedure. The CIP describes the pre-, peri- and -post procedural anticoagulation regimen to be followed. Imaging on the LA prior to the procedure to check on existing thrombus is a mandatory assessment in this CIP. These measurements in the CIP workflow should minimize the risk for thrombus formation.

Cardiac perforation/ Pericardial effusion/ Cardiac tamponade: Cardiac perforation may result from catheter manipulation or prolonged application of energy (risk is <1% for RF ablation and unknown for PF energy). Cardiac perforation may result in pericardial effusion or cardiac tamponade which requires percutaneous pericardial drainage or surgical repair.[3] Cardiac tamponade is a known complication of AF ablation and has a reported incidence of 0.2%-5%[41]. The occurrence of cardiac tamponade with PF technology is unknown. Physicians will be instructed to manipulate the catheter

carefully in order to avoid cardiac damage (such as mitral valve incompetence, valve injury), perforation or tamponade. In addition, the amount of power and force at any one location should be limited.

Coronary Artery Spasm: Limited clinical data has the raised potential for complication of coronary arterial spasm during PF ablation near the coronary arteries.[32,42, 43] Coronary artery spasm may lead to heart attack (ventricular tachycardia) and or chest pain.[33, 42, 44] Per CIP, when ablating near the coronary arteries (e.g. CTI region, mitral annulus), it is **REQUIRED** to ablate with RF energy using the study or a commercial RF ablation system.

Cerebral ischemic lesions: An Asymptomatic Cerebral Emboli (ACE) is defined as an occlusion of a blood vessel in the brain due to an embolus that does not result in any acute clinical symptoms and is therefore 'silent'. Emboli can result from thrombus, gas, air, tissue, or fat. Source of micro-emboli include thrombi, which can develop on sheaths, materials, air introduction through sheath or during catheter exchange. Additionally, the hazard of microbubble formation in pulsed field ablation, leads to an unknown level of risk of ACE.[43] According to HRS guidelines, 2017, incidence of ACE is expected in 2%-15% as a complication to AF ablation.[3, 41] However, literature on asymptomatic cerebral lesions after existing ablation modalities for AF (RF, Cryo) reports large variations between publications with rates that range from 2-40%.[3, 44-51] Recent publications on detection of asymptomatic brain lesions when using PF energy for AF ablation show a similar trend and present rates from 3-40%.[52-55] With either energy modality, the risk of ACE will be minimized by implementing an anti-coagulation regimen prior to catheter introduction into the LA and during procedure to avoid thrombi/emboli. To minimize the risk of air introduction, investigators will be trained on proper sheath handling, including removing air bubbles prior to insertion and will be instructed to minimize catheter exchange during the procedure.

Heart block: The application of RF energy close to the atrioventricular (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. The physician will be trained to closely monitor AV conduction during energy delivery and immediately terminate energy delivery if partial or complete AV block is observed, which will mitigate the risk for heart block. As per Instructions for Use, PF energy should not be used in close proximity to the AV node and extreme caution should be taken when delivering RF/PF energy in close proximity to the normal conduction system.

Vascular access / bleeding complication: Vascular access complication, femoral arteriovenous fistula, hematoma, and pseudoaneurysm are commonly reported in procedures requiring femoral access. Arterial or venous injury, including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other sites along the vessels occur in rare circumstances (risk <1%). These types of injuries may cause hemorrhage, hematoma or ischemic injury to an extremity or major organ. Hemorrhage could occur as a result of anticoagulation (risk <0.5%), which may require transfusion.[3] The risk of vascular access complication can be minimized by using a compatible sheath, vascular access techniques, ultrasound-guided access and appropriate anticoagulation management.

Radiation exposure: Radiation exposure during the fluoroscopic imaging of the catheters may result in an increase in the lifetime risk of developing a fatal malignancy (0.1%) or a genetic defect in offspring (0.002%).[45-47]The use of X-ray during the study procedure should be minimized or eliminated.

Infection: The percutaneous procedure carries risk of infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%).[48, 49] Risk can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents.[3]

Allergic, Anaphylactic and Toxic Reaction: A patient could develop an allergic reaction and/or inflammation due to the local anesthetic, sedatives, x-ray dye, heparin, protamine, or other agents administered during the procedure (risk <1%).[47, 50-54] The If an allergic reaction occurs, typical standard of care precautions should be taken. The product (s) should not be used where the packaging has been compromised, or already used, or reprocessed.

Ventricular Tachycardia, **Ventricular Fibrillation or other arrythmia**: The literature suggests that in some instances PF energy could induce ventricular tachycardia, ventricular fibrillation (ventricular rate usually >300 bpm), or another arrythmia induced by vagal response.[55-58] Care should be taken to carefully monitor the patient's ECG recordings throughout the procedure. Vagal responses (VRs) such as brady cardia, sinus arrest, and atrioventricular block frequently occur, and are known to happen (0.1%-0.4%) with both RF and PF technologies.[30, 59,60] Vagal responses may be associated with simultaneous modification of intrinsic cardiac autonomic nervous system expression. Extreme vagal response resulting in prolonged asystole should be treated using clinical standards of care. Pulsed field ablation may result in an extended pause in cardiac rhythm. Prior to delivering PF energy, **ensure** adequate preparations are in place to commence emergency ventricular pacing, administer CPR, or apply other measures consistent with standard of care should the need arise. Risk for ventricular tachycardia has been minimized by the design of the catheter and generator, which uses unipolar energy with very short duration of pulses. Care should be taken to thoroughly monitor the patient's ECG recordings throughout the procedure. Physicians will be instructed to be extra cautious when ablating near other anatomical structures such as ganglia.

Muscular Nerve Injury: Pulse field ablations have been associated with muscular contraction in the literature.[61, 62] These contractions can cause acute or post procedural patient discomfort. Patient comfort should be maintained through local pain management standards of care.

Hypervolemia/Fluid Overload: The STSF Catheter is an irrigated catheter. Excessive use of irrigation could cause hemodynamic imbalance. To prevent hypervolemia, ensure that the catheter is used per its instructions for use.

Risk due to Arcing: The hazard of arcing[63] of energy creates a risk for patient injuries including cardiac arrest, burns, papillary muscle rupture, valve rupture, or cardiac perforation. To prevent such harms, the physician should use the catheter and generator per their intended directions for use. To prevent the associated risks from arcing, do not operate the device in patients with metal cardiac implants or have metal in the same cardiac chamber with the ablation catheter.

Pulmonary injury: Pulmonary injuries, such as pneumothorax, may be caused by thermal injury during traditional RF injury.[64] As PFA is a minimally thermal modality, this injury is not expected to occur. However, to keep the risk of pulmonary injuries low, energy delivery should be halted after ECG signals have been sufficiently attenuated.[38]

In addition to the information in the IFU/UM and specific mitigation strategies for above mentioned potential risks, the criteria for subject selection, methods, personnel, facilities and training of the physicians are intended to minimize the risks to subjects undergoing this procedure.

Appropriate measures have been outlined in this study protocol to minimize the risk to subjects, while still providing the possible benefits (including but not limited to safety/effectiveness) of the treatment options to be studied.

Additional contraindications: Additional contraindications for pulse field ablation include: myxoma, prosthetic valves, history of myocardial infarction, implantable device such as a pacemaker, defibrillator, or other implanted metal cardiac device, and pregnancy.

6.2.2 Minimization of Risk

The criteria for subject selection, methods, personnel, facilities, and training that are 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 AEs (refer to section 13.1.2 for the Exclusion Criteria).[65]

Pre-procedure imaging: Subjects must have a pre-procedure Transesophageal Echocardiogram (TEE) or other imaging technique to screen for the presence of LA thrombus, which is intended to decrease the potential for thromboembolic complications.

Within procedure safeguards: Investigators highly skilled in intracardiac mapping and AF ablation with ablation catheters will be selected for participation in the study. AF ablation procedures will be performed in EP laboratories with the assistance of skilled nurses and technicians. Ablating investigators will undergo training, prior to enrolling subjects (refer to section 14.3.2).

Minimization of risk for the individual events:

- **Phrenic Nerve Paralysis (PNP):** by encouraging monitoring the PN with pacing maneuvers before and during ablation of the right sided PVs. Investigators are **REQUIRED** to ensure diaphragmatic capture prior to and post ablation when in the region of the right sided PVs. No new ablations should be delivered on or near the PN if evidence of PN impairment is observed and the catheter should be repositioned.
- **Pulmonary Vein Stenosis**: by proper placement of the catheter using a wide circumferential technique and by not positioning the study catheter within the tubular portion of the target PV.
- **Asymptomatic Cerebral Event (ACE)**: by implementing an anti-coagulation regimen prior to catheter introduction into the LA and during procedure to avoid thrombi/emboli. Investigators will be instructed to remove air bubbles prior to insertion and to minimize catheter exchange during procedure to mitigate the of risk air introduction.
- **Pericarditis**: by design, pulsed field energy is minimally thermal which should assist in minimizing the risk and by adhering to the device IFU.
- **Cardiac perforation, perfusion and tamponade events**: by limiting the amount of force and power at any one location and by training physicians and to use the study catheter as instructed.
- **Atrio-Esophageal Fistula, pulmonary injury** and **other related thermal events:** by the technology itself and encouraging the use of the lowest appropriate energy setting.

- **Coronary artery spasm:** by avoiding energy application near the coronary arteries and by physician training. Per CIP, when ablating near the coronary arteries (e.g. CTI region, mitral annulus), it is **REQUIRED** to ablate with RF energy using the study or a commercial RF ablation system.
- **Thrombi and hypervolemia:** by adhering to the use of irrigation settings per the catheter's Instructions for Use.
- **Ventricular tachycardia and other arrythmias:** by the design of the catheter, which uses biphasic energy with very short duration pulses. Physicians will be instructed to be extra cautious when ablating near other anatomical structures such as ganglia.
- **Heart block:** by closely monitoring AV conduction during energy delivery and immediately terminating energy delivery if partial or complete AV block is observed as per the catheter's instructions for use.
- **Vascular access complications:** by using clinical standards of care, and a study catheter compatible sheath.
- **Radiation exposure:** by using standard clinical practices to minimize or eliminate X-ray exposure during the procedure.
- **Infection:** by using standard aseptic technique and, when indicated, by the use of antibiotic agents.[38]
- **Allergic, Anaphylactic and Toxic reactions:** by not using product if the packaging has been compromised, or already used, or reprocessed.
- **Muscular contraction:** pain and discomfort due to muscular contraction can be mitigated through proper administration of pharmaceuticals for patient comfort.
- **Arcing** has been mitigated with the design of the generator. To further prevent the associated risks from arcing, do not operate the device in patients with metal cardiac implants

Post-procedural management: In accordance with the 2017 HRS/EHRA/ ECAS/APHRS/SOLAECE Expert Consensus[38] and the 2020 ESC AF Management Guidelines[66], all subjects will be recommended to be maintained on systemic oral anticoagulation therapy for at least two months 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 Safety Management Plan and reviewed periodically by a Data Monitoring Committee (DMC) as described in the DMC charter. An independent statistician will be responsible for conducting the interim analyses and reviewing the results with the designated DMC. A Clinical Events Committee (CEC) will be implemented to adjudicate primary safety endpoint events. The CEC will operate as described in the CEC Charter.

6.2.3 Known Potential Benefits and Risks

In patients with AF, elimination of or a reduction in symptoms is a major driving force for therapy. The primary clinical benefit of cardiac ablation of AF is an improvement in QoL resulting from the elimination of arrhythmia-related symptoms such as palpitations, fatigue, or effort intolerance.[3] Published animal and human studies demonstrate the potential for PF to be a safe and efficacious way to deliver energy for ablation via a non-thermal ablative modality.[43, 67] Influence on adjacent structures

has been previously studied. The additional benefit of tissue selectivity of PF energy reduces the risk of collateral tissue injury[43] of the well described complications in RF ablation techniques, the tissue specificity of IRE has been considered as a major advantage.[23]

Published animal and human studies demonstrate the potential for PF to be a safe and efficacious way to deliver energy via a non-thermal ablative modality.[68] PFA has an additional benefit of being tissue selective, which reduces risk of collateral tissue injury. PF energy can be applied selectively to cardiac cells, while preserving surrounding tissue.[69]

The TRUPULSE™ generator provides a novel approach for the treatment of cardiac arrythmias by enabling the use of both radiofrequency (RF) or pulsed field (PF) energy to produce targeted intracardiac lesions and achieve the intended therapeutic effect. The novel investigational device system is intended to treat atrial fibrillation with the theoretical potential while minimizing thermal collateral damage.

The commercial THERMOCOOL SMARTTOUCH SF™ catheter has been shown to be safe and effective for electrophysiological mapping and treating structures in the heart by obtaining electrograms, providing location information, and delivering RF energy during cardiac ablation procedures. As STSF is an established commercialized single tip catheter, it will apply no operator learning curve. The catheter has force-sensing technology that provides a real-time measurement of contact force (CF) between the catheter tip and the heart and low-flow rate Surround Flow (SF) irrigation, as stated in the product IFUs. CF sensing technology include feedback to the user on tissue contact to prevent inappropriate energy applications. Additional benefit of confirmed tissue contact includes efficient creation of 3D anatomical maps with CARTO® System and may translate to reduction of mapping fluoroscopy and procedure time.

Influence on adjacent structures has been previously studied. Of the well described complications in RF ablation techniques, the tissue specificity of IRE has been considered as a major advantage.[23]

Further reference can be made to the Risk Management Documentation for more information.

7. Study Device Description

The Biosense Webster Ablation System uses PF and RF energy to produce targeted intracardiac lesions for the treatment of atrial fibrillation in a process referred to as Pulse Field Ablation (PFA) and RF Ablation. The principal components of the system are the generator (TRUPULSE™) and the catheter (SMARTTOUCH THERMOCOOL™ SF) which, when used in conjunction with the CARTO™ system utilizing the VISITAG SURPOINT™ Module, provides electro- anatomical maps and catheter localization information for ablation. Additionally, the generator communicates with the nGEN™ pump to control irrigation fluid delivery to the catheter.

7.1 Device Acquisition

After obtaining a fully executed clinical trial agreement and appropriate approvals, the sponsor may initiate shipment(s) of investigational devices to the site. The Sponsor will keep records of all investigational devices shipped to the site. Approved investigational devices will be shipped directly to the site and will be received by the site. Site study personnel are responsible for appropriate logging of the devices received (i.e., lot numbers and quantity shipped), devices used in the study, disposition information regarding disposal or return to the Sponsor.

7.2 Device Storage and Stability

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

7.3 Instructions for Use

A copy of the IFU for Biosense Webster Ablation System is included in each product package.

7.4 Device Description and Specific Considerations

7.4.1 TRUPULSE™ Generator (D-1417-01- IC)

The TRUPULSE™ Generator is a specialized device that delivers two energy modalities: radiofrequency (RF) energy and pulsed field (PF) energy. The generator is designed for use with the compatible ablation catheter and with the Biosense Webster CARTO™ 3 System to enable catheter visualization and mapping. Additionally, the generator communicates with the nGEN™ Pump to control irrigation fluid delivery to the catheter.

The generator produces pulsed electrical field energy intended to destroy (ablate) arrhythmogenic intracardiac tissue by applying a series of short duration, high voltage, high frequency, unipolar or bipolar, biphasic pulses. When interfacing with the THERMOCOOL SMARTTOUCH™ SF catheter, the pulsed electrical field energy is delivered in unipolar mode via the indifferent electrodes (dispersive pads). The TRUPULSE™ Generator also incorporates the same functionality, mode of operation, control mechanism, and equivalent clinical performance as the nGEN™ Generator in RF energy delivery in power-controlled ablation mode. Both generators deliver RF energy based on user-configurable settings for power and duration, as well as real-time temperature feedback and impedance change during ablation.



Figure 1: Picture of the IRE Console

The TRUPULSE™ Generator system consists of following components:

- **Console:** The console contains the hardware that controls the delivery of energy.

- **Monitor:** The monitor contains a touch screen user interface. It also contains the software that communicates with the generator and external devices. The monitor allows the user to set parameters for the generator and control when energy is delivered. The monitor is connected directly to the console.
- **Pedal:** the pedal is an alternate way to start and stop ablation
- **Connection Interface Unit:** The CIU connects the catheter and indifferent electrodes and enables the interface to the CARTO™ 3 System PIU. The CIU also transmits signals to the CARTO™ 3 System, performs temperature measurements in both modes, and monitors contact quality of the indifferent electrodes.
- **Cables:** the cable connect the generator components to each other and to other devices

For a detailed listing of the system components and accessories can be found in the generator User Manual.

7.4.2 The THERMOCOOL SMARTTOUCH™ SF Bi- Directional Navigation Catheter (D-1348-05-SI-10)

The THERMOCOOL SMARTTOUCH™ SF Bi-Directional and Uni-Directional Catheters were placed on the EU market under Medical Device Directive (93/42/EEC) on April 12, 2010, and March 2, 2011, respectively. The catheters received CE mark authorization under Medical Device Regulation (2017/745) on May 1, 2022. In Canada, the THERMOCOOL SMARTTOUCH™ SF Bi-Directional Catheters were first licensed on January 20, 2015 (License 89000). The catheter is intended for use in cardiac electrophysiological mapping and, when used in conjunction with an RF generator, for cardiac ablation.

Biosense Webster intends to offer pulsed field energy as an alternative or adjunct to RF energy to the THERMOCOOL SMARTTOUCH™ SF Catheter with the TRUPULSE™ Generator.

No design change is required for the THERMOCOOL SMARTTOUCH™ SF Catheter for delivery of PF energy as an alternate or adjunct to RF for cardiac ablation. The THERMOCOOL SMARTTOUCH™ SF Catheter is labeled for clinical investigational use with the TRUPULSE Generator for this study.

The THERMOCOOL SMARTTOUCH™ SF Catheter is a multi-electrode luminal catheter with a deflectable tip designed to facilitate electrophysiological mapping of the heart and to transmit RF or PF energy to the catheter tip electrode for ablation purposes. The catheter shaft measures 7.5 F with 8 F ring electrodes. For ablation, the catheter is used in conjunction with a compatible generator and a dispersive pad (indifferent electrode). The catheter has force-sensing technology that provides a real-time measurement of contact force between the catheter tip and the heart wall.

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

At the proximal end of the catheter, a saline input port with a standard Luer fitting terminates from the open lumen. This saline port serves to permit the injection of normal saline to irrigate the tip

electrode. During ablation, heparinized normal saline is passed through the internal lumen of the catheter and through the tip electrode, to irrigate and cool the ablation site as well as the tip electrode. A compatible irrigation pump is used to control the saline irrigation. The catheter interfaces with standard recording equipment and a compatible generator via accessory extension cables with the appropriate connectors.

The catheter features a location sensor embedded in the tip section that transmits location and contact force information to the CARTO™ 3 System. An appropriate reference device is required for location reference position purposes. For information on using the catheter in mapping procedures and for information on appropriate reference devices, refer to the instructions for use for the CARTO™ 3 System. For further description of the operation of the irrigation pump, the generator, and the CARTO™ 3 System, refer to the applicable instructions for use or user manual.

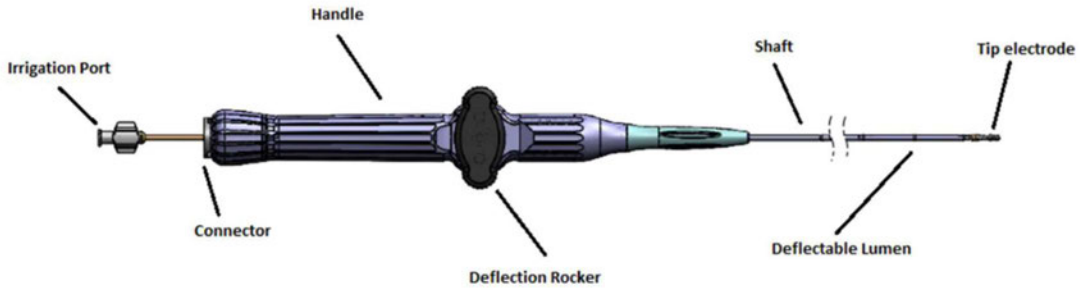


Figure 2: Picture of the THERMOCOOL SMARTTOUCH™ SF Bi-directional Navigation Catheter

7.4.3 System Components and Setup

To conduct an electrophysiology procedure, the THERMOCOOL SMARTTOUCH™ SF Bi-Directional Navigation Catheter and TRUPULSE™ Generator is used with the following Biosense Webster devices:

- nGEN™ Irrigation Pump (D-1397-01)
- SmartAblate Irrigation Tubing Sets (SAT001)
- Patient Interface Unit (PIU) of CARTO™ 3 system
- CARTO® 3 System V7.9 with PFA THERMOCOOL SMARTTOUCH® SF Support (CARTO® 3 V7.9.1, CARTO® 3 V7.9 Phase 1)
- Catheter Connection Cable (CR3434CT)
- BWI Mapping Catheter
- ≥8.5Fr Compatible Sheath

The following devices, are also required for the procedure:

- Electrophysiology (EP) Recording System
- Simulator
- Body Surface ECG Patches
- Indifferent electrode patches
- Electrocardiogram (ECG) Leads
- Fluoroscopy/X-Ray System
- Cardiac Defibrillator
- Intracardiac Ultrasound (Investigator preference, not required)

7.4.4 System Connectivity

Each site will have protocol-specified devices required for study participation. These devices must be used during the study to perform ablation procedures. Device set-up must be complete per the IFU and User Manual.

Below figures displaying a connectivity diagram from the front view (Figure 3) and back view (Figure 4) for system set up and a description of the connectivity respectively. The letters in Table 2 appear on the connection diagrams on the following pages.

Table 2: Cables

A	USB communication cable from console to monitor
B	Power supply cable from console to monitor
C	Pedal with attached cable
D	Cable connections for catheter
E	Ethernet cable from monitor to CARTO™ 3 Workstation, 25 m with Ethernet Isolator
F	Ethernet cable from monitor to CARTO™ 3 Workstation, 10 m with Ethernet Isolator
G	AC power cord from console to cart with snap ferrite
H	AC power cord from cart to mains with snap ferrite
I	Console to nGEN™ Pump cable
J	Interface box
K	Y-adaptor cable for STSF Catheter

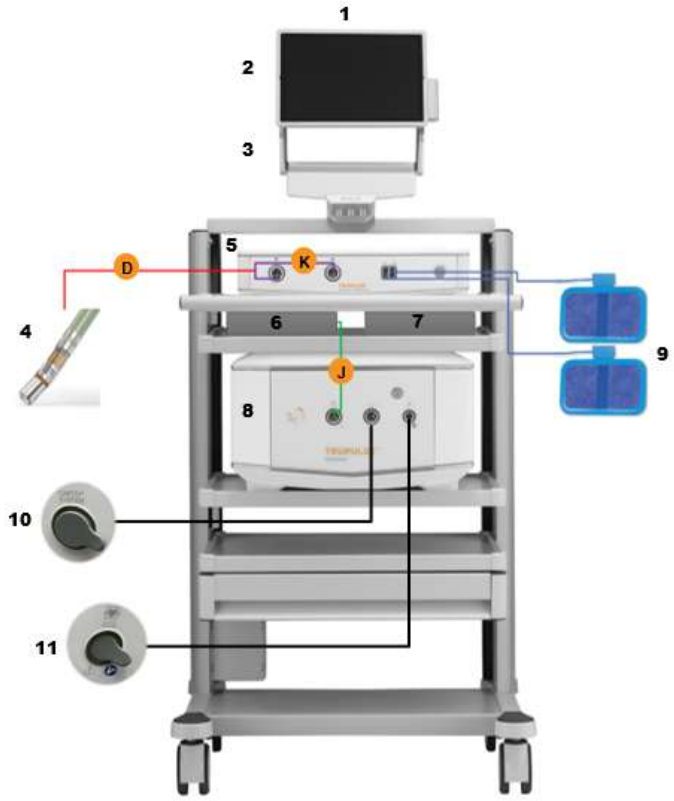


Figure 3: Connectivity diagram (front view) for system set-up

1	Monitor with docking station	7	CARTO™ Relay Box
2	Monitor, top cover kit	8	Console
3	Monitor arm	9	Indifferent electrodes
4	Catheter	10	Safety plug for CARTO™ connector
5	CIU	11	Safety plug for ECG connector
6	Interface Box		

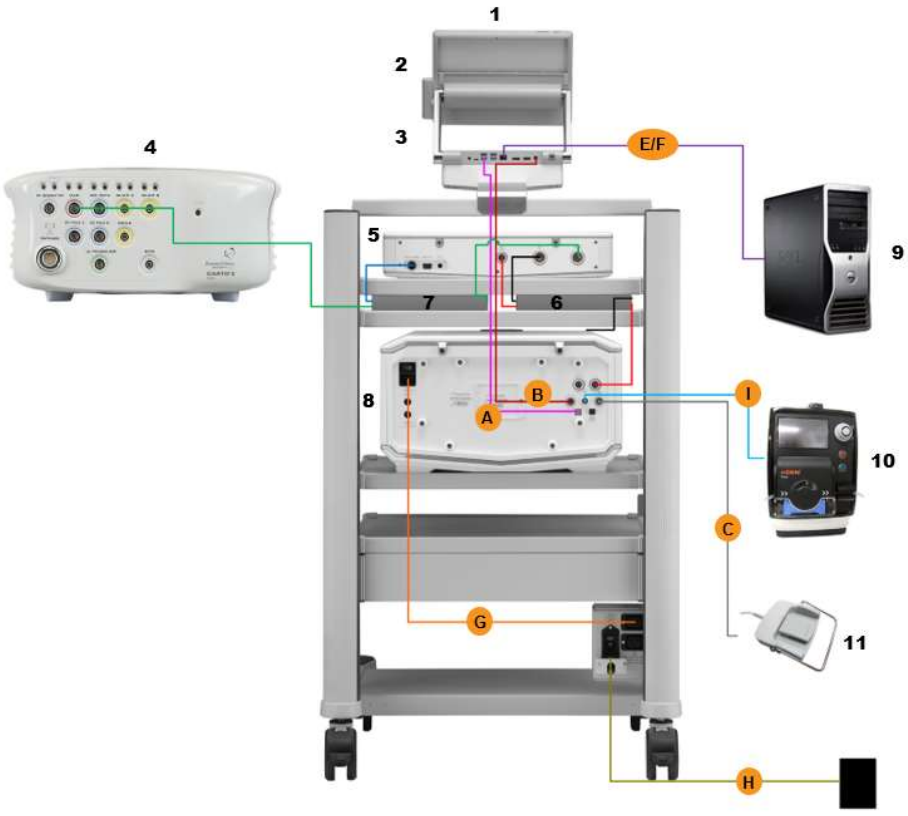


Figure 4: Connectivity diagram (back view) for system set-up

1	Monitor with docking station	7	CARTO™ Relay Box
2	Monitor, top cover kit	8	Console
3	Monitor arm	9	CARTO™ 3 Workstation
4	CARTO™ 3 System PIU	10	nGEN™ Pump
5	CIU	11	Pedal
6	Interface Box		

7.4.5 Required Study Devices

Table 3 lists the protocol-specified devices required for study participation. These devices must be used to perform the study ablation procedures. Device set-up must be completed per the IFU and User Manual.

Table 3: Required Study Devices

Investigational Devices	Function
THERMOCOOL SMARTTOUCH™ SF Bi-directional Navigation Catheter	Transmits energy to the target tissue.
TRUPULSE ™ Generator	Delivers PF and RF energy to compatible ablation catheter
Non-investigational Devices/Standard Equipment	**Function**
CARTO™ 3 SYSTEM V7.9.1 workstation	For mapping and visualization information with software for PFA and RF
nGEN™ Pump	Delivers heparinized saline to the catheter during the voltage application (D-1397-01)
CARTO™ 3 PIU	Patient Interface Unit for connectivity for therapeutic/diagnostic catheters and ultrasound.
Catheter Connection Cable (CR3434CT)	Connects the STSF Catheter with the TRUPULSE™ Generator.
SmartAblate Irrigation Tubing Sets (SAT001)	Delivers heparinized saline to the catheter during the voltage application
BW commercially available mapping Catheter	• Pre-ablation recording and mapping of the atria of the heart with the CARTO™ 3 System. • Confirmation of bidirectional block
≥8.5 Fr compatible sheath used commercially with STSF catheter.	Facilitate deployment of catheter into the atria.
Adhesive electrical dispersive pads/indifferent split electrode (with a surface area of ≥ 124 cm^2 that conform with IEC/EN 60601-2-2)	Component of the RF / PF current return path (Valley Lab recommended)
EP Lab Recording Equipment	Records multiple intracardiac electrograms and signals from the TRUPULSE™ Generator (power, temperature, impedance) and performs electrical stimulation.
Esophageal Temperature Monitoring Device (OPTIONAL)	Esophageal temperature monitoring

8. Ablation Procedure Guidelines

8.1 Energy and Ablation Selections

The TRUPULSE™ Generator is capable of controlling the delivery of RF and PF energy to the THERMOCOOL SMARTTOUCH™ SF catheter. The generator includes a touch screen that allows the user to select the energy type and apply ablations. Before energy delivery, verify RF or PFA is selected on the ablation screen. The start button contains a drag feature. After the start button is dragged or the pedal is pressed, there is a countdown until ablation begins. When the stop button is pressed or the pedal is released, the delivery of energy is terminated.

To perform RF ablation, the user selects target power and time from the ablation screen. The user may configure the cutoff temperature and warning temperature from the setup screen.

For more general operation of the TRUPULSE™ Generator, refer to the user manual for detailed information.

Functional parameters and user adjustable settings for the device(s) are presented in Table 4.

8.2 Ablation Parameters

When used with the THERMOCOOL SMARTTOUCH™ SF Catheter, the nGEN™ Pump will deliver a continuous infusion of 2 mL/min of room temperature heparinized saline (1u heparin/1 mL saline) when the catheter is in the left atrium. The recommended ablation parameters for the THERMOCOOL SMARTTOUCH™ SF Catheter are presented in Table 4.

Table 4: Ablation Parameters: PF and RF mode

	PF mode	**RF mode**	
Max. Power Settings/Max. Applications	24 applications	30W	31-50W
Max. Electrode Temp Limit (Celsius)	40Deg	40Deg	40Deg
Irrigation Flow	4ml/min	8ml/min	15ml/min
Max. Ablation Duration	26s	60s	60s
Max. Contact Force	40 grams	40 grams	

8.3 VISITAG SURPOINT™ Parameters

The VISITAG SURPOINT Module is a lesion quality marker that utilizes contact force, time, and power to calculate tag index values that are displayed on the CARTO® 3 system screen. The required parameter settings for the VISITAG SURPOINT™ Module are listed below in Table 5.

Table 5: CCI

CCI

9. Study Design

9.1 Description of the Study Design

The design of the study will be carried out as an interventional, prospective, multicenter, single-arm safety and effectiveness evaluation using the Biosense Webster Ablation System.

The study will enroll 135 subjects with drug refractory PAF who are candidates for atrial fibrillation ablation. All subjects will be followed for 12 months and scheduled for evaluation at 7 days, 1-, 3-, 6- and 12-month following index ablation procedure.

An early success interim analysis will be performed CCI [redacted] he study will declare early success if both primary safety and primary effectiveness endpoints are met at the early success interim analysis.

10. Study Objectives

10.1 Primary Objectives

The primary objective of this clinical investigation is to demonstrate safety and effectiveness of the BWI Ablation System when used for isolation of the atrial PVs in treatment of subjects with PAF. Specifically:

- To demonstrate safety based on early-onset Primary Adverse Events (PAEs) (within 7 days following the ablation procedure).
- To demonstrate 12-month effectiveness off AAD based on the freedom from documented (symptomatic and asymptomatic) atrial arrhythmia (Atrial Fibrillation (AF), Atrial Tachycardia (AT) or Atrial Flutter (AFL)) episodes based on electrocardiographic data (12-lead ECG or ≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365).

10.2 Secondary Objective

The secondary objective of this clinical investigation is to evaluate Quality of Life (QOL) up to 12 months.

10.3 Additional Objectives

The additional objectives of this study are to evaluate acute procedure success, procedural data, the incidence of (procedure and/or device related) serious adverse events during and after procedure up to 12 months.

11. Study Endpoints

11.1 Primary Endpoints

Acute Safety

The primary safety endpoint is the occurrence of Primary Adverse Events (PAEs) within seven (7) days of an ablation procedure (including the initial and repeat procedures) which uses the BWI Ablation System.

PAEs include the following Adverse Events (AEs):

Esophageal perforating complications (e.g., Atrio-Esophageal Fistula[1], esophago-pericardial fistula,…)	Phrenic Nerve Paralysis (permanent)[5]
Cardiac Tamponade[2, 3]/perforation[2]	Pulmonary Vein Stenosis[6]
Device or procedure related death[4]	Stroke/CVA[7, 8]
Major Vascular Access Complication/Bleeding	Thromboembolism
Myocardial Infarction	Transient Ischemic Attack (TIA)
Pericarditis	Heart Block
Pulmonary Edema (Respiratory Insufficiency)	Vagal Nerve Injury/Gastroparesis[9]

[1]Atrio-esophageal fistula occurring up to 90 days post AF ablation process procedure will be considered a PAE.
[2]Cardiac Tamponade/Perforation occurring up to 30 days post AF ablation process procedure will be considered a PAE
[3] Hemodynamic compromise or instability is defined as Systolic BP < 80 mm Hg.
[4]Device or procedure-related death anytime during or after the ablation procedure and any death reported within 30 days of ablation procedure where device and/or procedure relatedness cannot be determined via CEC adjudication
[5] Absent phrenic nerve function as assessed by a sniff test.
[6] Pulmonary Vein Stenosis occurring anytime during the 12 month follow up period will be considered a PAE.
[7] Non-focal global encephalopathy requires unequivocal evidence based upon neuroimaging studies to be reported as a stroke
[8] Modified Rankin score assessments should be made by certified individuals.
[9] Vagal nerve injury is considered to be a major complication if it requires or prolongs hospitalization, or results in ongoing symptoms for more than 30 days following an ablation procedure.

Primary Effectiveness

The primary effectiveness endpoint is achieving freedom from documented (symptomatic and asymptomatic) atrial tachyarrhythmia (AF, AT or AFL of unknown origin+) episodes based on electrocardiographic data (12-lead ECG or ≥30 seconds on ECG or sponsor provided Holter device) during the effectiveness evaluation period (Day 91-Day 365) and freedom from the following failure modes:

- Acute procedural failure, including:
  - Failure to achieve entrance block in all pulmonary veins using the investigational device (except those that are silent and/or cannot be cannulated post-procedure) by the end of the procedure

CCI [redacted]

- Repeat ablation failure, including:
  - More than 1 repeat ablation procedures for AF/AT/ AFL (of unknown origin+) during the 3-Month Blanking Period (Day 0-90 post index procedure).
  - Any repeat ablation procedure for AF/AT/ AFL (of unknown origin+) during the evaluation period.

- Non-study device failure, including:

  - Use of a non-study device to treat PV targets to achieve isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) during index or repeat procedure in the blanking period.
  - Use of a non-study device for ablation in the left atrium during either index or repeat procedure within the blanking period.

- AAD failure:
  - Taking a new AAD (Class I & III) for atrial tachyarrhythmia (AF, AT or AFL of unknown origin+) or taking a previously failed Class I/III AAD after the 3-month follow-up visit window (i.e., any time beyond Day 104 to 365 post index procedure).
  - Oral amiodarone is prescribed/taken post index ablation procedure.

- Continuous AF/AT/AFL of unknown origin[+] on a standard 12-lead ECG during the effectiveness evaluation period.

- Any DC cardioversion procedure during the evaluation period for documented atrial tachyarrhythmia (AF, AT or AFL of unknown origin[+]) recurrences ascertained through protocol specified arrhythmia monitoring methods (12-lead ECG, Holter).

C [redacted]
C [redacted]

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11.2 Secondary Endpoints

QOL Improvement: Atrial Fibrillation Effect on Quality-of-Life (AFEQT) Questionnaire will be used to assess the quality-of-life post ablation procedure. The endpoint is the change in quality of life, as measured by the total AFEQT score, at 12-month post procedure, in comparison to baseline assessment.

11.3 Additional Effectiveness Endpoints

The following additional effectiveness endpoints will be assessed:

- Acute procedural success: the achievement of electrical isolation for all PVs which is evidenced by the confirmation of entrance block at the end of the procedure. Use of solely RF mode for PV isolation, resulting from study device malfunction leading to a failure in PF energy delivery is also deemed a failure.
- Acute reconnection: the restoration of electrical conduction in the targeted veins, which is identified by adenosine/isoproterenol challenge.
- First pass isolation: the achievement of entrance block in targeted veins after the first encirclement, which is evaluated prior to the adenosine challenge
- Ablation by a non-study device for PVI (Touch-up): Use of non-study device for touch-up ablation to achieve PV isolation in all clinically relevant targeted PVs
- Repeat ablation procedures for left atrial arrhythmia (AF, AT or AFL of unknown origin*) within the 12-month FU period will be assessed. The evaluation will include the timing of repeat ablation (blanking period or after blanking), any reconnections of targeted PVs from the index procedure, and the type of arrhythmia treated during the repeat ablation, along with their corresponding targets.

- 12 Month Single Procedure Treatment Success: freedom from documented symptomatic atrial tachyarrhythmia (AF, AT or AFL of unknown origin+) episodes based on electrocardiographic data (12-lead ECG or ≥30 seconds on ECG or sponsor provided Holter device) during the effectiveness evaluation period (Day 91-Day 365) following a single index ablation procedure, and freedom from the following failure modes:
    - Acute procedural failure: Failure to achieve entrance block in all pulmonary veins using the investigational device (except those that are silent and/or cannot be cannulated post-procedure) by the end of the procedure
    - Non-study device failure: use of a non-study device to treat pulmonary vein targets to achieve isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated)during the index procedure.
    - Any repeat ablation procedure for AF/AT/AFL (of unknown origin+) post the index procedure.

- 12-Month freedom from symptomatic recurrence: freedom from documented symptomatic atrial tachyarrhythmia (AF, AT or AFL of unknown origin+) episodes based on electrocardiographic data (12-lead ECG or ≥30 seconds on ECG or sponsor provided Holter device) during the effectiveness evaluation period (Day 91-Day 365).

- Hospitalization for cardiovascular events: the impact of ablation procedure on CV hospitalization 12M after the index procedure, in comparison to the hospitalization history prior to enrollment

- DC Cardioversion: the impact of ablation procedure on the number of receiving DCCV 12M after the index procedure, in comparison to the history of DCCV prior to enrollment

- AAD Utilization: utilization of Class I/III antiarrhythmic drugs during the follow-up, in comparison to the baseline AAD use

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11.4 Additional Safety Endpoints

Safety

- Occurrence of Serious Adverse Device Effects (SADEs)
- Occurrence of Unanticipated (Serious) Adverse Device Effect (UADEs and USADEs)
- Occurrence of non-serious adverse events (non-SAEs)
- Occurrence of device and/or procedure related Serious Adverse Events (SAEs) within 7 days (early-onset), 8 to 30 days (peri-procedural) and >30 days (late onset) of initial ablation procedure

11.5 Procedural Data

Procedural data, including but not limited to

- Total procedure time (from first femoral puncture to last catheter out)
- PVI time
- PF/RF application time
- Mapping time

- Number of PFA/RF applications by left and right PV
- Total fluoroscopy time
- Fluid delivered from the study catheter
- Total study catheter left atrial dwell time
- Ablation parameters per application ((e.g., temperature, power, impedance, contact force (CF), PF or RF, RF power, PF/RF tag index per segments etc.)
- VISITAG SURPOINT™ values (Tag Index) per segment
- Power Range
- CF Range
- Use of paralytics and type of anesthesia
- Device Deficiency Information (if applicable)

12. Health Care Utilization Data

Health care utilization pre-, during and post-hospitalization for the study index ablation procedure, as well as any additional hospitalizations during the study period will be collected.

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

13. Study Population

Patients scheduled to have a clinically indicated ablation procedure for the management of their drug refractory PAF will be screened for enrollment per the study's inclusion and exclusion criteria. The "investigation population" (meeting all inclusion and exclusion criteria) represents the "target population" (drug resistant PAF subjects) indicated for catheter ablation per consensus guidelines, in addition the criteria listed below ensure mitigation of risks (as per instructions for use and user manual) associated with the patients' health status at the time of screening and contraindications for study assessments (as specified further in this CIP).

13.1 Subject Selection

The study consists of a PAF population. Subject selection varies as described below.

13.1.1 Inclusion Criteria

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

1. Diagnosed with Symptomatic PAF (Physician's note indicating recurrent self-terminating AF). At least one (1) electrocardiographically documented AF episode within twelve (12) months prior to enrollment. Electrocardiographic documentation may include, but is not limited to, electrocardiogram (ECG), Holter monitor, or other electrocardiographical devices accepted by investigators.
2. Failed at least one (1) Class I or Class III AAD as evidenced by recurrent symptomatic AF or has intolerable side effects or is contraindicated to the Class I or Class III AAD.
3. Age 18 - 80 years.
4. Able and willing to comply with all pre-procedure, post-procedure, and follow-up testing and visit requirements.
5. Willing and capable of providing consent.

13.1.2 Exclusion Criteria

Candidates will be excluded if ANY of the following criteria apply:

1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause (e.g., documented obstructive sleep apnea, acute alcohol toxicity, morbid obesity (Body Mass Index >40 kg/m^2), renal insufficiency (with an estimated creatinine clearance < 30 mL/min/1.73 m^2) ….).
2. Previous LA ablation or surgery
3. Patients known to require ablation outside the PV region (atrioventricular reentrant tachycardia, atrioventricular nodal reentry tachycardia, atrial tachycardia, atrial flutter of unknown origin, ventricular tachycardia and Wolff-Parkinson-White).
4. Previously diagnosed with persistent AF (> 7 days in duration)
5. Severe dilatation of the LA (documented LAD >50mm antero-posterior diameter on imaging within 6 months prior to enrollment
6. Documented left atrium (LA) thrombus within 48 hours prior to the index procedure by TEE, or by ICE prior to transeptal puncture during procedure.
7. Documented severely compromised LVEF (LVEF <40%) by imaging within 6 months prior to enrollment
8. Uncontrolled heart failure or New York Heart Association (NYHA) Class III or IV
9. History of blood clotting, bleeding abnormalities or contraindication to anticoagulation (heparin, warfarin, or dabigatran)
10. History of a documented thromboembolic event (including TIA) within the past 12 months, or history of a documented left atrial appendage (LAA) thrombus
11. History of a documented symptomatic lacunar infarction within the past 12 months
12. Previous PCI/MI within the past 2 months
13. Coronary Artery Bypass Grafting (CABG) surgery within past 6 months
14. Valvular surgery, cardiac surgery (e.g., ventriculotomy, atriotomy) or valvular cardiac (surgical or percutaneous) procedure.
15. Unstable angina pectoris within the past 6 months
16. Anticipated cardiac transplantation, cardiac surgery or other major surgery within the next 12 months.
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 severe chronic symptoms
18. Known significant PV anomaly that in the opinion of the investigator would preclude enrollment in this study
19. Has known pulmonary vein stenosis
20. Pre-existing hemi diaphragmatic paralysis
21. Acute illness, active systemic infection or sepsis
22. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes catheter introduction or manipulation.
23. Severe mitral regurgitation (Regurgitant volume 60 mL/beat, Regurgitant fraction 50%, and/or Effective regurgitant orifice area 0.40cm2)
24. Presence of implanted pacemaker, Implantable Cardioverter-Defibrillator (ICD), recently implanted (within 6 months) LAAO device or other implanted metal cardiac device within the cardiac space that may interfere with the energy field created during the ablation procedure.
25. Presence of a condition that precludes vascular access (such as IVC filter)
26. Significant congenital anomaly or a medical problem that in the opinion of the investigator would preclude enrollment in this study

27. Categorized as vulnerable population and requires special treatment with respect to safeguards of well-being
28. Current enrollment in an investigational study evaluating another device or drug.
29. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of childbearing age and plan on becoming pregnant during the course of the clinical investigation.
30. Life expectancy less than 12 months
31. History of massive hemorrhage within the past 6 months.
32. Presenting contra-indications for the devices

13.1.3 Subject Enrollment and Retention

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

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

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

To ensure generalizability of results and minimize the influence of any single site, no more than 25% of the total enrollment will be allowed at a single site for both study populations.

13.1.4 Subject Disposition

Disposition and accountability of the study subjects will be summarized descriptively for the subject categories defined as following:

- **Enrolled Subjects:** Patients who sign the ICF.
- **Excluded Subjects:** Subjects who are enrolled but never undergo insertion of the study catheter. Excluded subjects will be subjected to safety event reporting between ICF signature and date of exclusion. Subjects who signed the ICF but are found to be ineligible prior to insertion of the catheter are also considered as excluded.
- **Evaluable Subjects:** All enrolled subjects who have the study catheter inserted.
- **Discontinued Subjects**: Evaluable subjects who have the catheter inserted, but do not undergo ablation (i.e., no energy is delivered with the study catheter).
    - Discontinued subjects will remain in follow-up for 3 months post catheter insertion.
    - Discontinued subset subjects are not subjected to the additional subset assessments.

- If an SAE is reported for a discontinued subject, the subject will be followed until event resolution (with or without sequelae), stabilization, or until the event is adequately explained.

- **Lost to Follow-up Subjects:** Evaluable subjects of which contact is lost after most recent visit (despite 3 documented attempts to contact the subject). If the subject does not respond to the 3 telephone calls, then the investigator must send a certified letter to 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, withdrawn, terminated early, or lost-to-follow-up from the study prior to the final study visit.

13.2 Subject Withdrawal/Early Termination

13.2.1 Reasons for Withdrawal or Early termination

Subjects may withdraw from the clinical investigation at any time without penalty or loss of benefits to which they may otherwise be entitled. The decision for the subject to withdraw informed consent must be made independently of influence by the investigator or site personnel.

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

- Any clinical 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
- 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 follow-up period.

13.2.2 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) and the applicable on-site source documentation. If the subject is withdrawn due to an AE or 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 can be replaced. Replacement subjects will be recruited and enrolled following the same procedures as non-replacement subjects.

14. Responsibilities

14.1 Investigator Responsibilities

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

Specific responsibilities include:

- Obtaining EC approval and renewals
- Providing Sponsor with:
    - Written EC approval letters and EC approved consent forms,
    - Signed, dated Investigator Agreement,
    - Signed and dated Financial Disclosure form at study outset and any time financial changes occur, for up to one year following completion of the study
    - Curriculum vitae for each Investigator and key research staff member
    - Copy of current medical license for each study investigator, as applicable
- Maintaining an accurate and current Delegation of Authority Log which identifies all individuals authorized to perform work for the study at each site
- Completing appropriate training on the study device and the study protocol prior to enrolling and treating subjects
- Maintaining accurate and current logs for the study as requested by the study team, including but not limited to:
    - Subject screening log
    - Device Accountability log
- Obtaining informed consent (including privacy language) from patients prior to subject participation
- Performing the ablation procedure as described in the protocol
- Complying with the clinical protocol
- Notifying the Sponsor and EC of adverse events, deaths, device failure/malfunctions and deviations as defined in this protocol and per EC requirements
- Notifying Sponsor promptly of withdrawal of EC approval
- Complying with EC (as applicable) and Sponsor annual report requirements
- Completing eCRFs accurately and as soon as possible after collection of data
- Reviewing and signing designated eCRFs in a timely manner
- Maintaining relevant source documentation and allow Sponsor direct access to perform monitoring and auditing duties
- Immediately notify the Sponsor of any pending Regulatory Authority audits/inspection at the study site and allow access to study records for authorized regulatory entities
- Complete all subject follow-up visits, including efforts to maintain contact with subjects who fail to comply with the follow-up schedule. Before a subject may be classified as ‘lost to follow-up’, the Investigator or authorized personnel should document 3 attempts to contact the subject.
- Retaining study records as described in Section 24.2. The Sponsor will notify the Investigator when records may be destroyed.
- Preparing a final report and periodic EC updates as required.

14.2 Sponsor Responsibilities

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

- Preparing study documents including but not limited to the protocol, eCRFs, Investigator Brochure and template informed consent
- Completing pre-study site assessments and approvals
- Obtaining approval from applicable regulatory agencies
- Obtain signed study contracts from investigators/hospitals, contract research organizations, or other involved parties.
- Providing protocol and device training to investigators and research personnel, as applicable
- Instructing operators and technicians in the proper use and monitoring of study devices
- Monitoring the study throughout the duration of the investigation
- Securing investigator/site compliance with the protocol and applicable regulations
- Creation and maintenance of eCRF database
- Conducting all communications with applicable regulatory agencies
- Submitting study supplements for regulatory approval (e.g., request for study expansion), as necessary
- Preparing reports summarizing the status of the clinical study no less often than annually, which will be supplied to applicable regulatory agencies. Annual reports may also be provided to the Principal Investigator
- Preparing and submitting the final clinical study report to the applicable regulatory agencies
- Having AEs reviewed by the study specific committees and/or study specific reviewers, as required
- Report (including AE's and DDs) to study investigators and regulatory agencies, as required

14.3 Training

14.3.1 Research Team Training

The training of appropriate clinical site personnel will be the responsibility of the Sponsor or the Sponsor's representative. In some cases, training may be performed by an existing site staff member who has already been trained by the Sponsor (e.g., assigning a new CRC to the study).

Prior to initiating subject enrollment at a site, appropriate study training will be provided. To ensure uniform data collection and protocol compliance, the Sponsor will present a formal educational session to study site personnel that will include review of the Clinical Study Protocol, techniques for the identification of eligible subjects, instructions on in-hospital data collection, follow-up schedules, and regulatory requirements.

Remote as well as on-site contacts will be used to monitor study performance indicators such as enrollment compliance, data submission rate, data errors, protocol questions, and GCP compliance. The sponsor will reinforce the training or provide clarification throughout the study, as needed.

14.3.2 Investigator Training

Prior to initiating subject enrollment at a site, appropriate study training will be provided. Investigators selected to participate in the study will be experienced in intracardiac mapping and AF ablation with focal ablation catheters. In addition to research team training outlined above,

Investigators will undergo didactic and hands-on device (TRUPULSE™ Generator) training in accordance with the physician training charter.

15. Study Medication

The following medications are applicable for this CIP:

PRIOR to the procedure
Uninterrupted anticoagulation management for at least 3 weeks prior to ablation procedure is **MANDATORY** for each study subject.

- For subjects on warfarin/coumadin therapy, subjects **MUST** be maintained on warfarin/coumadin for at least 3 weeks prior to treatment with an INR ≥ 2 (To be confirmed weekly for 3 weeks prior to procedure. A reading must be taken within 48 hours prior to procedure). Any INR < 2 within 3 weeks prior to ablation will lead to exclusion of the subject or postponement of the study procedure until the INR is ≥ 2 for at least 3 weeks prior to treatment (the subject will need to be reconsented if treatment is scheduled for >90 days after original consent date). The results must be available prior to start of procedure.

- Anticoagulation therapy should not be interrupted or stopped prior to the procedure (this means no doses should be missed or omitted) and daily regimen should be continued. One dose can be omitted on the evening prior- or day of procedure as per standard of care.

DURING the procedure

The procedure sequence is provided in the Study Ablation Procedure Guidelines (section 16)

FOLLOWING the procedure

- Anticoagulation therapy is **REQUIRED** for at least 2 months following ablation.
  - Anticoagulation therapy in such patients should be administered in accordance with the AHA/ACC/HRS 2014 Guideline for the Management of Patients With Atrial Fibrillation (January CT, Wann LS, Alpert JS et al. AHA/ACC/HRS 2014 Guideline for the Management of the Patients With Atrial Fibrillation. Circulation 2014: 130:2071-2014).
- Decisions regarding continuation of systemic anticoagulation beyond 2 months post ablation should be based on the subject's stroke risk profile.
- Per HRS guidance systemic anticoagulation is recommended be continued beyond two months post-procedure in subjects with a CHA2DS2-VASc score of ≥ 2 (unless deemed contraindicated based on clinical considerations).
- Additional medications needed to treat clinical indications are at the discretion of the clinical investigation physician.

15.1 Antiarrhythmic Drugs

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Table 6: CCI

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16. Study Procedures and Evaluations

16.1 Patient Screening

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

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

16.2 Informed Consent

The Patient ICFs used must have approval from the Sponsor and the study site's EC prior to patient enrollment in the study. An approved Patient ICF may be translated as appropriate. A copy of the blank approved Patient ICF must be maintained by each investigator in the designated study administrative file.

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

The informed consent will include an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and as required per local regulations. Subject confidentiality will be maintained throughout the clinical trial in a way that assures that individual subject data can be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows identification of all data reported for each subject. Data relating to the trial may be made available to third parties, provided the data are treated as confidential and that the subject's privacy is guaranteed.

16.3 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 90 days of consent)
- **Demographics** (age, gender, etc).
- **Vital signs** (height, weight, etc.)
- **NYHA** Functional Class Scale
- **CHA_2DS_2 VASc Score** Subjects will be scored against the CHA_2DS_2 VASc
- **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).
- **Cardiovascular Hospitalization history**: information on hospitalization for cardiovascular reason (including arrhythmia, cardioversion, …) from 12 months prior to enrollment will be collected from medical records and recorded in the eCRF.
- **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 anticoagulation management for at least 3 weeks prior to ablation procedure is **mandatory** for each study subject. For subjects on warfarin/coumadin therapy, subjects must be maintained on warfarin/coumadin for at least 3 weeks prior to treatment with an INR ≥ 2 (to be confirmed maximum 48 hours pre-procedure). Any INR < 2 within 3 weeks prior to ablation will lead to exclusion of the subject or postponement of the study procedure until the INR is ≥ 2 for at least 3 weeks prior to treatment (the subject will need to be reconsented if treatment is scheduled for >90 days after original consent date). The results must be available prior to start of procedure. NOTE: If a subject is receiving warfarin/coumadin therapy and the anticoagulation therapy is changed to heparin or an equivalent agent due to documented elevated INR, this will be considered continuous anticoagulation therapy and the subject may proceed with the study procedure even if the INR falls below 2 while the subject is still receiving alternate therapy.
- **Physical Exam**: Exam should be performed by a physician or equivalent (NP or PA) prior to the ablation procedure.
- **Pregnancy test** within 24 hours prior to the procedure): pre-menopausal women only
- **Imaging to determine LA size and LVEF:** Imaging is required to determine the atrial size prior to the AF procedure. A Transthoracic Echocardiogram (TTE) is allowable imaging modality to determine LA size and LVEF. If the subject has undergone an imaging procedure (CT, MRI or ICE or TEE) within the last 6-months where the atrial size (parasternal long axis view) and LVEF were assessed and documented, the pre-procedure imaging assessment is not required.
- **Imaging for detection of LA thrombus** (performed within 48 hours of the study procedure or day of ablation procedure prior to study catheter insertion). The following are allowable imaging modalities:

- TEE
- Intracardiac Echocardiography (ICE)

- **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.
- **Baseline Quality-of-Life (QoL) Assessment** (AFEQT™) questionnaire

16.4 Study Ablation Procedure Sequence

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

PREPARATION of the ablation procedure:

- Anesthesia or sedation should be delivered per standard EP lab procedure. It is recommended to ensure presence of anesthesiologist during the procedures.
- **REQUIRED:** Placement of two indifferent electrodes on the patient prior to mapping
- Esophageal monitoring/localization (investigator discretion) with CARTOSOUND® and/or ICE, barium swallow or temperature probe (CIRCA™ or Single Thermistor™ probes ONLY)
- CARTO™ Respiratory gating recommended (unless using Jet Ventilation)
- Introduce an Intracardiac Echo (ICE) probe to review LA anatomy and PVs (at investigator discretion)
- Diagnostic catheter placement:
  - Coronary sinus catheter in the CS for pacing purposes is recommended
  - Other catheters may be placed at the discretion of investigator
- **REQUIRED:** Pace the phrenic nerve in the SVC prior to ablations to confirm diaphragmatic capture.
- **REQUIRED:** Administration of heparin bolus before or immediately following transseptal puncture
- A double or single transseptal puncture should be performed per standard EP lab (at the discretion of the investigator).
- Cardioversion if subject is in AF (at discretion of investigator)

MAPPING prior to the ablation procedure:

- **REQUIRED:** Creation of a left atrial anatomical map, including PV anatomy prior to ablation, utilizing a multi-electrode BWI mapping catheter, Lasso®, PentaRay®, or OctaRay.
  - Additional imaging techniques such as 3D rotational angio (at investigator discretion), or CT integration can be used to supplement the map.
  - A pre-ablation voltage map may be created at physician discretion
- **REQUIRED**: pace the phrenic nerve prior to ablation in the region of the right sided PV's in order to evaluate the proximity of ablation catheter to phrenic nerve. If phrenic capture is present utilize PF energy to perform PVI for the right sided veins (anteriorly)
  - If phrenic capture is not present, utilize RF energy on the anterior portion and PF energy on the posterior portion of the right sided PVs.

ABLATION Procedure:

- **REQUIRED:** Confirmation of ACT ≥300 seconds PRIOR to start of ablation with investigational catheter
  - ACT should be targeted to be maintained ≥300 seconds throughout the ablation.
  - ACT level must be checked on regular basis while investigational device is in the left atrium.
  - If ACT is below 300 seconds, systemic anticoagulation with heparin should be administered (except for any safety reasons) to ensure an ACT target of 300 seconds without pausing ablation procedure.
- **REQUIRED:** Introduction of the 8.5 Fr or greater compatible sheath, if not used for mapping. Before inserting the sheath into the patient, flush the sheath with heparinized normal saline to remove air bubbles.
- Introduce the investigational THERMOCOOL SMARTTOUCH™ SF catheter as per IFU.
- **NOTE**: When using a diagnostic device in the same chamber as ablation device, ensure that the device is not in close proximity to the ablation catheter.
- Advance and position the THERMOCOOL SMARTTOUCH™ SF Catheter at the targeted PV.
- When position is satisfactory, commence energy delivery with the investigational catheter per recommended workflow.

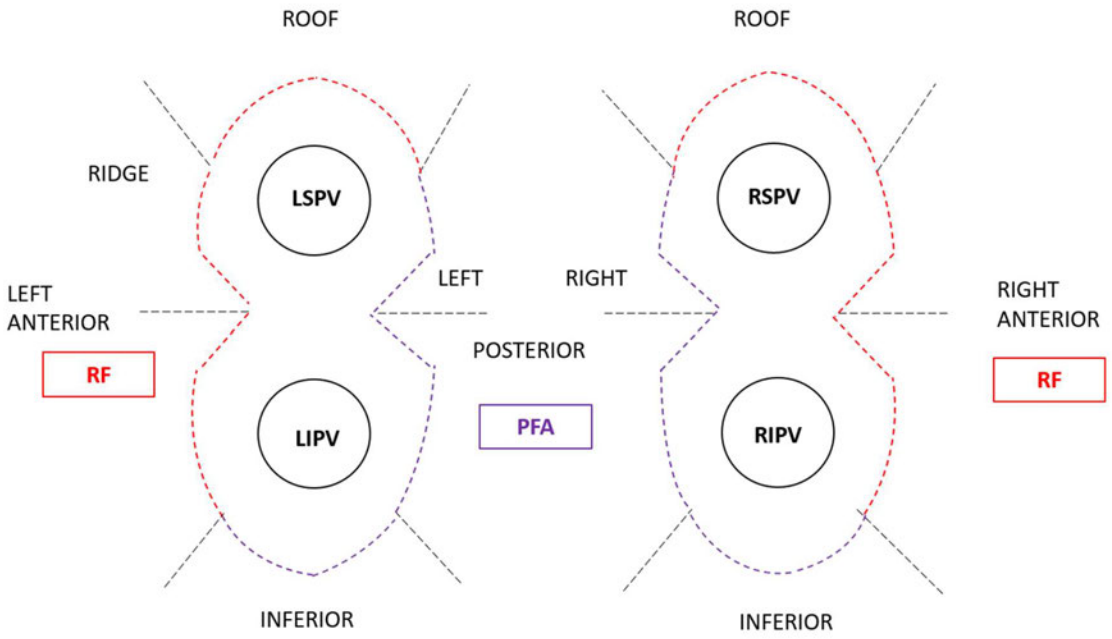
Pulmonary Vein Isolation (PVI) Procedure:

- Use point-by-point ablation to obtain a contiguous lesion set for ipsilateral PV isolation.
- **REQUIRED**: Utilize the PF ablation index (when using Pulsed field energy) and RF ablation index (when using RF energy) to deliver lesions around the pulmonary veins.
  - The target index values for PF and RF are indicated in Table 7:

Table 7: CCI

CCI

Figure 5. Ablation Strategy



- All subjects will undergo PV ablation with the investigational device until PVI is achieved in all targeted PV's:
  - ONLY after an investigator determines they are unable to achieve PVI with the investigational device, a commercial (RF) system can be used to complete the procedure (PVI only).
- **REQUIRED:** Confirmation of entrance block (PVI) of all clinically relevant targeted PVs
  - **REQUIRED:** Administer adenosine/isoproterenol for each clinically relevant targeted PV to rule out dormant conduction
    - In case touch up ablations are needed; it is strongly recommended that the energy utilized matches the primary energy used in the initial PVI ablation as noted in Table 7. If these touch up ablations do not achieve entrance block, the physician can elect to change the energy source but **MUST** still target the PF or RF index values as listed in Table 7.
  - **REQUIRED:** Confirmation and documentation of final entrance block (exit block is optional) (PVI) of all clinically relevant targeted PVs
    - To verify entrance block, analyze electrograms in coronary sinus and/or atrial paced rhythm to confirm that no PV potentials are present.
    - Use a BWI multi-electrode, LASSO® or PENTARAY® NAV Catheter or OCTARAY® NAV mapping catheter for confirmation per investigators choice.
- The ablation procedure is considered complete when confirmation of entrance block in clinically relevant targeted PVs is confirmed.

Special Scenarios

- **REQUIRED:** Prior to ablation in the anterior region of the right sided PVs pace to evaluate the proximity of ablation catheter to phrenic nerve. If phrenic capture is present utilize PF

energy to perform PVI for the right sided veins (anteriorly) in order to minimize risk of phrenic nerve injury.

- **NOTE:** The target index value when utilizing PF energy on the anterior is 550 (Table 7).

Post Pulmonary Vein Isolation:

- **REQUIRED**: after last application or confirmation of final entrance block (exit block is optional) at the right sided PVs, evaluate diaphragmatic capture while pacing the phrenic nerve. NOTE: In cases of deep sedation a fluoroscopic evaluation of the diaphragm may be used.
  - Subjects whose post-procedural evaluation of the diaphragm demonstrates diaphragmatic paralysis should undergo appropriate follow-up test (e.g. sniff test or inspiration/expiration chest radiography) at discharge and subsequent follow-up visits until resolution of the diaphragmatic paralysis or the completion of the study (diaphragmatic paralysis is considered to be permanent when it is documented to be present 12 months).

- A post paced activation and bipolar voltage map may be created at physician discretion and if SOC.

Ablation outside the PV region

- **Prophylactic ablation** of empirical sites and outside the PV region (e.g. SVC, PW, roofline) is **NOT** allowed.
- CCI [redacted]
- If an arrhythmia other than AF is spontaneously induced/triggered or other AF targets require ablation outside the PV, RF energy should be utilized with the investigational system.
- A post-ablation voltage map may be created at physician discretion and if standard of care.
- The post ablation steps will follow the standard of care practice at the site.

16.4.1 Collection of Ablation Procedure Data for Post-Analysis

At the completion of the study ablation procedure, two back-up copies of the CARTO™ case, CARTO™ error files and generator system 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 provided to/collected by the Sponsor.

16.4.2 Data Collection during Study Ablation Procedure

The following information will be collected during the procedure, including but not limited to:

Technical parameters are collected via CARTO™ datafiles and generator files, including but not limited to:

- Number of PF/RF applications
- Ablation locations/targets
- Energy delivered
- PF/RF application time

- Ablation parameters per application ((e.g., temperature, power, impedance, contact force (CF), PF or RF, RF power, contact force, PF/RF tag index per segments etc.)
- VISITAG SURPOINT™ values (Tag Index) per segment
- Power Range
- CF Range
- Ablation information will be collected in the CARTO™ 3 system and investigational Generator
- Contact force values

Other procedural parameters are collected via Electronic Data Capture (EDC), including but not limited to:

- Use of a non-study catheter for PVI
- Number of PF/RF applications per target PV, total and by subject
- Number of PF/RF applications required with a non-study catheter
- PVI confirmed with BWI multi-electrode mapping catheter
- PV acute reconnection (early or dormant)
- Procedure time (from first femoral puncture to last catheter out)
- Mapping time (start mapping - end mapping)
- Total fluoroscopy time
- Total study catheter LA dwell time (from first study catheter insertion in LA until study catheter removal from LA)
- ECG data
- Total fluid delivered via study catheter
- Total fluid delivered via intravenous line (if captured)
- Fluid output (if captured)
- Device deficiency information (if applicable)
- Procedural medication (paralytics)
  Use of paralytics and type of anesthesia

16.4.3 Pre-Discharge Assessments

The following should be performed prior to hospital discharge:

- Physical exam: Exam should be performed by a physician or equivalent (NP or PA).
- MUST be performed pre-discharge.
    - If physical exam demonstrates new abnormal neurological findings as compared to the one performed at baseline, a formal neurological consult and examination with appropriate imaging (i.e., DW-MRI) needs to be done to confirm or rule out any suspected diagnosis of stroke.
        - Diagnosis of stroke/CVA must be confirmed by at least one of the following:
            - Neurology or neurosurgical specialist
            - Neuroimaging procedure (MR or CT scan or cerebral angiography)
            - Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage)
            - Stroke: (diagnosis as above, preferably with positive neuroimaging study)
                - Minor—Modified Rankin score <2 at 30 and 90 days
                - Major—Modified Rankin score ≥2 at 30 and 90 days

- MRS assessments should be made by certified individuals

- AFL/AT/AF recurrence
- Electrocardiogram (12-Lead ECG)
- Transthoracic Echocardiogram (TTE), for evaluation pericardium for possible pericardial effusion and/or pericarditis. In the event significant pericardial effusion is identified, subjects should be followed until the condition resolves.
- Cardiac-related concomitant medications (such as AADs, anticoagulation regimen, etc.) All cardiac-related medications prescribed since the ablation procedure till the end of follow-up will be recorded, including the type and name of the medication, associated indications, starting and ending dates of the prescriptions, etc.
- Documentation of Adverse events (if any)

16.5 Post-Ablation Follow-up Schedule

The subject will be required to complete follow-up visits through 12 months post initial ablation procedure. Follow-up visits should be scheduled according to the following timeframes: 7 day +3 days (7-10; phone call or clinic visit), 1 month, ±7 days (1M Day 23-37), 3 month ±14 days (3M, Day 76-104), 6 month, ±30 days (6M, Day 150-210), and 12 month, ±30 days (12M, Day 335-395). Follow-up visit schedule should be based on the date of the index ablation procedure and will not reset if a subject undergoes a repeat AF ablation procedure.

16.5.1 Seven (7) Day Follow-Up Visit

Seven (7) Day, +3 day (Day 7-10) post ablation procedure must be done to assess:

- Adverse Events; if any
- Change in medication regimen
- AFL/AT/AF recurrence; if any
- Subject discontinuation form; if applicable (12-Month)

16.5.2 Monthly Follow-Up Visit

At 1, 3, 6 and, 12-month follow-up visits, the following assessments will be performed:

- **Physical Exam (Clinic Visit)** Exam should be performed by a physician or equivalent (NP or PA).
- **Quality of Life questionnaire (Clinic Visit):** AFEQT™ are to be collected at the 3M, 6M, and 12M visits.
- **Electrocardiogram; 12-Lead ECG (Clinic Visit):** Data from 12-lead ECG recordings will be collected at the 3M, 6M and 12M follow-up visits. Collect at 1M visit if available as standard of care. The completed ECGs post blanking period will be reviewed and adjudicated by an independent expert physician.
- **24 Hour Holter:** Holter monitor will be used at the 3M, 6M and 12M follow-up visits to monitor the subjects' heart rhythm for 24 hours continuously. A core lab will be utilized to evaluate and assess the 24-hour Holter recordings.
- **Adverse Events (Clinic Visit/Phone Call):** AEs must be collected from the time the subject signs the informed consent onwards.

- At each follow-up visit, data to be collected may include, but is not limited to repeat ablation procedure and/or procedures resulting from the ablation procedure, outpatient visits, and ER visits.

- **AFL/AT/AF recurrence (Clinic Visit/Phone Call)**
  - All evaluable subjects will undergo arrhythmia monitoring (e.g., ECG and HM) per the protocol defined monitoring schedule in Section 16.10 and Table 8.
  - For subjects with AFL recurrence identified through Holter monitoring, a 12 Lead ECG MUST be collected.
- **Medication Review (Clinic Visit/Phone Call):** Changes to any cardiac related medications (cardiac related (anti-arrhythmia drugs, anticoagulation regimen, etc.) shall be collected
- **Repeat Ablation (Clinic Visit):** Any ablation procedure performed after the index procedure will be recorded at 3M, 6M, and 12M follow-up as well as at any unscheduled visits.
- **Subject Completion/ Discontinuation Form (Clinic Visit/Phone Call)**: At 12-Month or any time the subject discontinued from the study

16.6 Repeat Ablation Procedures

Repeat procedures may be performed at the discretion of the investigator. It is highly recommended to collect arrhythmia documentation (in example documented recurrences) before performing a repeat procedure.

Repeat procedures during the blanking period (≤ 90 days post index ablation procedure) must be conducted with the investigational device, with or without focal touch-up, if the arrhythmia is due to PV triggers. Procedures for CTI dependent flutter in the follow up period are not considered repeat procedures per CIP.

Repeat procedures performed after the blanking period (≥91- 365days post index ablation procedure) may be managed per investigator discretion using a commercially available ablation catheter and generator.

For the repeat procedures, the investigator must collect and provide information on location of reconnections of PVs and in case of atrial flutter recurrence, confirm if CTI dependent flutter or not. Procedures for CTI dependent flutter in the follow up period are not considered repeat procedures per CIP, if the CTI lines is not ablated in the index procedure. The follow-up schedule will remain based on the index ablation procedure.

16.7 Early Termination Visit

If a subject withdraws/loss to follow up/early terminates from the study or dies prior to completion of the 12- month visit, follow the assessments as provided in Table 8 and complete the Subject Completion/ discontinuation form.

16.8 Unscheduled Visit

If a subject returns for a potential study related cardiovascular or neurological visit outside of the protocol-defined visit schedule provided in Table 8, 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.

16.9 Core Laboratory for Evaluation

Independent core laboratories will be used to review the Holter Monitors for the objective evaluation of recurrence of atrial tachyarrhythmias.

16.10 Heart Rhythm Monitoring

ECG and Holter Monitors will be used to monitor the subjects' heart rhythm post-treatment.

Holter Monitors:
Subjects will be provided with a Holter monitor and instructions for the 24-hour recording, no later than at the 6-month follow-up visit. 24-hour recordings will be obtained at the 3-month, 6-month and 12-month time periods.

16.11 Schedule of Events Table

Table 8 displays the required schedule for subject treatments and evaluations.

Table 8: Summary of Subject Visits and Assessments

	Pre-Procedure	Ablation/ Discharge		Phone/ Virtual	Follow-Up Visits				
	Screening / Baseline	Study Abl[1] Day 0	D/C	7 D D7-10	1 M D23-37	3 M D76-104	6M D150-210	12M D335-395	UNS
Visit no.	1	2	3	4	5	6	7	8	90
Informed consent[1]	X								
Inc & Excl Criteria	X								
Demographics	X								
Vital Signs	X								
Physical Exam	X		X		X	X	X	X	X
Med History[2]	X			X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Hospitalization/ CV history	X								
AF History	X								
12-Lead ECG	X[3]		X		X[3]	X	X	X	X[3]
Adverse Events[4,5]	X	X	X	X	X	X	X	X	X
CHA_2DS_2-VASc and $CHADS_2$ Score	X								
NYHA Scale	X								
QOL Assessment[6]	X					X	X	X	
Pregnancy Test[7]	X								
LA size and LVEF imaging[8]	X								
LA Thrombus Imaging[9]	X								
Ablation Assessments		X							
Device Deficiency		X							
TTE[10]			X						
Concomitant Medications[11]	X	X	X	X	X	X	X	X	X
Repeat Ablation[12]				X	X	X	X	X	X

	Pre-Procedure	Ablation/ Discharge		Phone/ Virtual	Follow-Up Visits				
	Screening / Baseline	Study Abl[1] Day 0	D/C	7 D D7-10	1 M D23-37	3 M D76-104	6M D150-210	12M D335-395	UNS
Visit no.	1	2	3	4	5	6	7	8	90
AF/AT/AFL recurrence			X	X	X	X	X	X	X
24 Hr Holter[13]						X	X	X	
Completion/ discontinuation form[14]		X	X	X	X	X	X	X	

1 Initial ablation procedure should be done within 90 days of consent.

2 Medical history including but not limited to arrhythmia, AAD therapy, and thromboembolic events. In subsequent visits, medical history is collected to confirm no changes in medical history since last visit.

3 Data from 12-lead ECG recordings will be collected, if available. For pre-procedure, can be performed before ICF signature.

4 AEs collected once consent has been signed. Collected to confirm no changes in health status since last visit.

5 If AE results in hospitalization, data should be collected.

6 Quality of life tools (AFEQT).

7 Pregnancy test must be done on pre-menopausal women only, within 24 hours of the procedure.

8 Imaging within 6 months prior to procedure to assess the LA and LVEF. In case the imaging assessment is older than 6 months, LA/LVEF dimensions shall be re-measured during the index procedure prior to insertion of the study catheter.

9 Subjects must undergo imaging (using one of the following modalities TEE or ICE) to rule out the presence of LA thrombus within 48 hours of the ablation procedure.

10 All subjects will undergo TTE prior to discharge to evaluate pericardial effusion.

11 Concomitant medication: only cardiac (i.e., anti-arrhythmia drugs, anticoagulation regimen, etc.) & index procedure related (i.e., adenosine, anticoagulation, pain medication)

12 Information on any repeat ablation after the index procedure will be collected.

13 Arrhythmia monitoring via 24H Holter, site to contact subject and verify if any symptoms experienced during the Holter monitoring.

14 12-month visit/last completed visit or last data collection

17. Assessment of Safety

17.1 Adverse Event Recording

17.1.1 Definition of Adverse Events (AE)

An Adverse Event (AE) means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the study device or ablation procedure(MDR Article 2(57)).

NOTE:

a. This definition includes events that are anticipated as well as unanticipated events

b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

- The following clinical events will not be considered an adverse event for this clinical study:
  - Any medical condition that is present at the time of screening. Such conditions should be added to the medical history if not previously reported. However, if the study subject's condition deteriorates at any time during the study, it should be recorded as an AE.

- The following clinical events will not be considered an adverse event for this clinical study but will be captured in the database separately:
  - Recurrence of pre-existing AF/AT/AFL of unknown origin+

- AF/AFL of unknown origin+/AT recurrence requiring direct current cardioversion during the blanking period or pharmacological cardioversion (and accompanying hospitalization) at any time throughout the duration of the study. However, new onset of left atrial flutter occurring post-ablation is an AE. For subjects with AFL recurrence identified through Holter monitoring, a 12 Lead ECG MUST be collected.
- Recurrence of pre-existing or underlying (treated during index procedure) AFL/AT is considered as a recurrence of disease
- Onset of non-previously identified AFL/AT which is treated during the index procedure as underlying arrhythmia (pre-existing condition)
- Re-ablation for AF or any pre-existing AFL/AT, however any procedural complication is considered an AE and shall be reported within the applicable timelines.
- Re-ablation for any non-pre-existing (underlying) AFL/AT which is treated during the index procedure, however any procedural complication is considered an AE and shall be reported within the applicable timelines.
- Cardioversion (pharmacological or synchronized electrical) for AF/AFL/AT recurrence during the hospitalization for the index ablation procedure, or throughout the duration of the study.

- CCI [redacted]

17.1.2 Definition of Serious Adverse Event (SAE)

A SAE is any event that led to any of the following:

- Death
- Serious deterioration in the health of a subject that resulted in any of the following:
  - Life-threatening illness or injury
  - permanent impairment of a body structure or a body function
  - In-patient hospitalization or prolongation of patient hospitalization*
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function
  - Chronic disease
- Fetal distress, fetal death or a congenital physical or mental impairment 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 but should nevertheless be included in routine study reporting. *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 visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.*

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 (section 1716.9). Investigators will determine, at each encounter, whether any adverse events (AE) have occurred, and judge their seriousness and relationship to the study device and procedure. Each investigator shall provide anonymized source documentation as requested by the Sponsor to facilitate reporting and adjudication of these events.

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

CCI

17.1.3 Primary Adverse Event

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

A Primary AE is one of the following events occurring within seven (7) days following an AF ablation procedure with the THERMOCOOL SMARTTOUCH™ SF (STSF) when used with the TRUPULSE™ Generator per protocol. Table 9 provides the PAEs and their descriptions.

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

Table 9: Primary Adverse Events

Primary Adverse Event	Description / Criteria
Death[1]	Subject death related (definitely, probable, possible) to the device or procedure and occurs at any time during or after the procedure. Any death reported within 30 days of ablation procedure where device and/or procedure relatedness cannot be determined via CEC adjudication
Esophageal perforating complications (Atrio-Esophageal Fistula[2], esophago-pericardial fistula)	Defined as a connection between the atrium and the lumen of the esophagus or connection between pericardium and lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophagus erosion combined with evidence of a fistulous connection to the atrium or pericardium and lumen of the esophagus 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 esophageal perforation complications.
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

Primary Adverse Event	Description / Criteria
	-Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Cardiac Tamponade[3,4]/Perforation [3]	The development of a significant pericardial effusion during or within 30 days of undergoing the index or repeat procedure during blanking period with investigational system. 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
Thromboembolism	Formation of a clot (thrombus) inside a blood vessel causing obstruction to blood flow accompanied by clinical symptoms. 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.
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). [5] -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).

Primary Adverse Event	Description / Criteria
	Definition: Stroke: (diagnosis as above, preferably with positive neuroimaging study) Minor—Modified Rankin score <2 at 30 and 90 day[6] Major—Modified Rankin score ≥2 at 30 and 90 days
Transient Ischemic Attack (TIA)	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 h), always within 24h; neuroimaging without tissue injury.
Phrenic Nerve Paralysis	Absent phrenic nerve function as assessed by a sniff test. A phrenic nerve paralysis is considered to be permanent when not resolved at the final follow-up (i.e., 12-month visit or longer).
Pulmonary Vein Stenosis[7]	A reduction of the diameter of a PV or PV branch. Severe PV stenosis (≥70% reduction in the diameter of the PV) will be considered a PAE and major complication of AF ablation.
Major Vascular Access Complication /Bleeding	Major Vascular Access Complication: Development of a hematoma, an AV fistula or a pseudoaneurysm which requires intervention, such as surgical repair or transfusion, prolongs hospitalization[8] by more than 48h, or requires hospitalization[8]. Major Bleeding: Requires and/or treated with transfusion or results in a 20% or greater fall in hematocrit.
Pericarditis	Pericarditis should be considered a major complication following ablation if it results in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization[8] by more than 48 hours, requires hospitalization[8], or persists for more than 30 days following the ablation procedure.
Heart Block	Impairment of AV conduction requiring intervention (e.g., temporary or permanent pacemaker) due to iatrogenic cause (e.g. inappropriate energy application, traumatic maneuvering of catheter or other intracardiac devices)
Pulmonary Edema (Respiratory Insufficiency)	Respiratory insufficiency resulting in pulmonary complications necessitating intubation or other significant intervention (including diuretics administered specifically for treating pulmonary edema or ICU hospitalization requiring oxygen administration but not intubation). Exclusion criteria include: •Pneumonia – infiltrate, fever, and leukocytosis •Acute Respiratory Distress Syndrome
Vagal Nerve Injury/ Gastroparesis	Injury to the vagal nerve that results in esophageal dysmotility or gastroparesis. Vagal nerve injury is

Primary Adverse Event	Description / Criteria
	considered to be a major complication if it prolongs hospitalization[8] by more than 48h, requires hospitalization[8] or results in ongoing symptoms for more than 30 days following an ablation procedure.

1 Device or procedure-related death anytime during or after the ablation procedure and any death reported within 30 days of ablation procedure where device and/or procedure relatedness cannot be determined via CEC adjudication
2 Atrio-esophageal fistula occurring up to 90 days post AF ablation process procedure will be considered a PAE.
3 Cardiac Tamponade/Perforation occurring up to 30 days post AF ablation process procedure will be considered a PAE
4 Hemodynamic compromise or instability is defined as Systolic BP < 80 mm Hg.
5 Non-focal global encephalopathy requires unequivocal evidence based upon neuroimaging studies to be reported as a stroke
6 Modified Rankin score assessments should be made by certified individuals.
7 Pulmonary Vein Stenosis occurring anytime during the 12 month follow up period will be considered a PAE.
8 "Hospitalization" means the event necessitated an admission to a health care facility e.g., with at least an overnight stay. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.

17.1.4 Non-Serious AEs

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

17.1.5 Anticipated AEs

An anticipated AE 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 Aes that are reasonably anticipated to occur during the cardiac EP procedure are listed in the table in Appendix 3, including standard of care practice. The probability of occurrence may vary as it depends on technique used, patient selection, operator and hospital experience. The published clinical studies reported lower complication rates than real-world data. [3] [70] An increase of overall incidence of complications associated with atrial fibrillation (AF) ablation was observed from 5.3% in 2000 to 7.5% in 2010 (In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures).[64]

The table below includes the incidence of the complications of AF ablation reported in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation.[3]

Table 10: The incidence of the complications of AF ablation

Anticipated Adverse Event	Incidence*
Air embolism	<1%
Asymptomatic Cerebral Emboli (ACE)	2%-15%
Atrio-Esophageal fistula	0.02%-0.11%
Cardiac tamponade	0.2% to 5%
Cardiac Coronary artery stenosis/occlusion	<0.1%
Death	<0.1%-0.4%
Gastric hypomotility	0%-17%
Mitral valve entrapment	<0.1%

Anticipated Adverse Event	Incidence*
Pericarditis	0%-50%
Permanent phrenic nerve paralysis	0% to 0.4%
Pulmonary vein stenosis	<1%
Radiation injury	<0.1%
Stiff left atrial syndrome	<1.5%
Stroke and TIA	0% to 2%
Vascular complications	0.2% to 1.5%
* Data from 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation[3]	

These events should be reported via EDC as anticipated Aes. Anticipated AEs are to be reported to the sponsor via EDC as indicated in section 17.

17.1.6 Unanticipated (Serious) Adverse Device Effect

An Unanticipated Adverse Device Effect (UADE) or Unanticipated Serious Adverse Device Effect (USADE) is any (S)AE 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, outcome, or degree of incidence in the current 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 Appendix 3 for a comprehensive list of foreseeable and anticipated AEs. An investigator shall submit to the reviewing EC a report of any unanticipated adverse device effect occurring during an investigation per EC requirements.

17.1.7 Study Device Deficiency, Failure or Malfunction

A device has failed if it does not perform according to the instructions for use or fails to meet the expectations of the device and/or investigator (i.e., related to appearance of the device, performance, durability, safety, effectiveness, quality, reliability, labeling, etc.). If a device failure is detected or suspected, it should be documented on the appropriate CRF and the device must be promptly returned according to the Sponsor's instructions. If the device failure is associated with an AE, both the device failure and AE must be reported to the Sponsor immediately upon awareness (refer to Section 19.2).

17.2 Reporting Requirements

17.2.1 Adverse Event Documentation and Reporting Requirements

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

The Sponsor is responsible for reviewing AEs (e.g., causality, classification, seriousness) and for ongoing safety evaluations in accordance with the study safety management plan. In case of disagreement between the Sponsor and the principal investigator(s) that remain after query resolution, the Sponsor shall communicate both opinions to the concerned parties.
The Sponsor will ensure that investigators are instructed to return devices suspected of causing an AE or SAE (i.e., definitely device-related, probably device-related, or possibly device-related) in accordance with relevant regulations and current company procedures.

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

Timing for reporting the different types of AEs is described in Table 11.

Table 11: 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
Study device failure/malfunction that could have led to a SAE *	Report to Sponsor immediately upon awareness of event but no later than 72- hours
All other Adverse Events	Report to Sponsor immediately upon awareness of event but no later than 2 weeks

* If a) suitable action had not been taken, or b) intervention had not been made or, c) if circumstances had been less fortunate.

17.2.2 Intensity/Severity of Event

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

Table 12: 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.

17.2.3 Causality

Causality of AEs is defined as follows:

Table 13: Adverse Event Causality Classifications (Ref. MDCG 2020-10/1 guidance)

Relation	Definition of Relation to device/procedure
Causal Relationship	The adverse event is associated with the investigational device or with procedures beyond reasonable doubt when:

	– The event is a known side effect of the product category the device belongs to or of similar devices and procedures, – The event has a temporal relationship with investigational device use/application or procedures, – The event involves a body-site or organ that o the investigational device or procedures are applied to, o the investigational device or procedures have an effect on, – the adverse event follows a known response pattern to the medical device (if the response pattern is previously known); the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the adverse event (when clinically feasible) – other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out. – harm to the subject is due to error in use, – the event depends on a false result given by the investigational device used for diagnosis, when applicable.
Probable	The relationship with the use of the investigational device or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
Possible	The relationship with the use of the investigational device or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Not Related	Relationship to the device or procedures can be excluded when: – the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device, – the adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible, – the discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the adverse event, – the event involves a body-site or an organ that cannot be affected by the device or procedure, – the adverse event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); – the event does not depend on a false result given by the investigational device used for diagnosis, when applicable,
To establish the non-relatedness and/or relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the adverse event	

17.2.4 Outcome

AE outcomes are assessed according to the following classifications:

Table 14: Adverse Event Outcome Classifications

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

17.2.5 Adverse Event Documentation

All AEs must be documented on the appropriate eCRF. All AEs must be monitored until they are adequately resolved or stabilized, with follow-up reports submitted to the Sponsor or designee as soon as new information becomes available. For certain events, anonymized documentation, such as a written event narrative detailing the clinical course, copies of correspondence with the local EC, hospital records, death certificates, and autopsy reports, may be requested by the Sponsor or designee. Follow-up information relative to the subject's subsequent course must be submitted to the sponsor or designee until the event has resolved or, in case of permanent impairment, until the condition stabilizes. If the subject is withdrawn from the study because of the AE, the information must be included on the appropriate eCRFs.

17.3 Safety Oversight

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

17.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be constituted to monitor subject safety and provide guidance on study adaptation. The DMC charter will document the constitution, roles and responsibilities of the committee. Under the rules of an approved study-specific charter, safety data will also be reviewed by an established DMC which may recommend appropriate action(s) to ensure subject safety.

17.5 Clinical Events Committee

A Clinical Events Committee (CEC) will be implemented to adjudicate the primary safety endpoint events. The CEC will operate as described in the CEC Charter.

18. Deviations from Clinical Study Plan

The investigator is responsible for ensuring that the clinical investigation is conducted in accordance with the procedures described in this protocol except in medical emergencies. A protocol deviation is defined as an instance of failure to follow, intentionally or unintentionally, the requirements of the protocol (e.g., missed test or procedure, visit out of window, non-adherence to inclusion/exclusion criteria). Investigators are not allowed to deviate from the protocol. Protocol deviations will be monitored closely and may require reporting to the EC and/or regulatory authority per EC/regulatory authority requirements.

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

In emergencies, prior approval for a protocol deviation will not be required, but the Sponsor clinical operations personnel should be notified as soon as possible. The study monitors shall verify that the conduct of the study is in compliance with the currently approved protocol and applicable regulations and shall identify any issues of non-compliance with regulations or guidelines. Issues of non-compliance include but are not limited to repeated protocol deviations, failure to obtain proper informed consent, non-conformance to EC requirements, and failure to report any event requiring expedited reporting. EC must also be notified promptly of significant protocol deviations as they are defined by the EC.

Non-compliance and issue escalation will be addressed per the study Project Operations Manual.

19. Investigational Device Accountability

19.1 Investigational Device Acquisition and Accountability

The study site will receive the necessary amount of study-related materials prior to commencement of study ablation procedure. Study-related devices (investigational and non-investigational) will be shipped to the site after completion of required documentation (essential regulatory documents, Clinical Trial Agreement, EC approval, regulatory agency approval) and training. Investigational study devices are only to be used for subjects enrolled in this clinical study. Study-related materials may be augmented throughout the study on an as-needed basis.
The Sponsor will label all devices as “Investigational Device” (as applicable for the region) in a prominent location. All system installations will be performed by trained field services personnel according to internal processes.

The Sponsor will keep records of all investigational devices shipped to the site. Investigational site personnel are responsible for appropriate logging of devices received (i.e. lot numbers and quantity shipped), devices used in the study, disposition information regarding disposal or return to the Sponsor.

The site Device Accountability Log will include the following information:

- Date of receipt
- Individual acknowledging receipt
- Quantity received
- Catalog number for catheters
- Serial/lot numbers
- Expiry Date
- Dates devices were used
- Subject IDs for whom devices were used
- Reason for return (i.e. used without incident, malfunction, expired, end of study, …)
- Date of return (as applicable)
- Type of disposal (i.e., return to Sponsor for adverse event, complaint, expired, end of study, etc.)

19.2 Device Returns

All investigational devices (used and unused) will be returned to the Sponsor's attention and per Sponsor's Instructions. Device deficiencies should be properly documented on the eCRF. Any suspected malfunctioning device or device associated with an AE (device related or probably/ possibly device related) should be returned immediately to the Sponsor and will undergo a thorough complaint analysis.

Returned devices must be decontaminated per hospital policy (if applicable) and labeled with the following information:

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

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

ATTN: Complaints Lab
C. G Laboratories, Inc.
2449 Bob White Drive
Granbury, TX 76049 USA

20. Administrative Responsibilities

20.1 Audits and Inspections

The sponsor and/or designee and/or Regulatory Authority (TGA, Health Canada) may contact the participating institution to inform the investigator of an upcoming audit/inspection. The investigator should immediately notify the sponsor of any regulatory 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.

21. 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 as soon as possible after collection via eCRF. Missing or unclear data will be corrected as necessary throughout the trial. The Sponsor may request further documentation such as physician and/or cardiac EP lab procedure notes when complications or malfunctions are observed and reported. Specific monitoring requirements are provided in the study monitoring plan.

21.1 Early Termination Monitoring Visit

If early termination of the study is required, each site will undergo a monitoring visit as described in the monitoring plan to conclude any outstanding issues, collect all outstanding CRF information, verify device accountability, and discuss any other items relevant to the conclusion of the study. Subjects will be notified of the termination of the study. Any enrolled subjects will continue to be followed per the study protocol requirements until a study closeout plan is implemented that outlines alternative follow-up procedures.

22. Statistical Methodology

The Sponsor will be responsible for the overall analysis of data from this CIP and an independent statistician will be responsible for conducting the early success interim analyses and reviewing the results with the designated DMC. Detailed statistical analysis methods planned for this study will be described in the Statistical Analysis Plan (SAP). A brief statistical overview of key statistical analyses is provided below.

22.1 Study Design

This is a prospective, single arm, multi-center, clinical evaluation of the Biosense Webster Ablation System to evaluate safety and effectiveness of the system for the treatment of Paroxysmal Atrial Fibrillation (PAF).

22.2 Treatment Assignment

All subjects will undergo index ablation procedures using the Biosense Webster Pulsed Field (PF)/Radiofrequency (RF) Ablation System.

22.3 Primary and Secondary Endpoints and Associated Hypotheses

I. Primary Safety Endpoint

The primary safety endpoint for a subject is defined as having Primary Adverse Events (PAEs) (within 7 days of an index ablation procedure (including the initial and repeat procedures) which uses the investigational STSF catheter and TRUPULSE™ generator per clinical investigation plan). The definition of PAE can be found in section 17.1.3 of the study protocol.

To evaluate the primary objective of the study, the PAE rate will be compared against a performance goal (PG) of 12%. The formal hypotheses to test the primary safety endpoint is given as follows:

$$H_0: P_S \geq 0.12$$

$$H_a: P_S < 0.12$$

where P_S represents the primary adverse event rate.

II. Primary Effectiveness Endpoint:

The primary effectiveness endpoint (PEE) for a subject is defined as freedom from documented (symptomatic and asymptomatic) atrial tachyarrhythmia (AF, AT or AFL of unknown origin+) episodes based on electrocardiographic data (12-lead ECG or ≥30 seconds on sponsor provided Holter device) during the effectiveness evaluation period (Day 91-Day 365) and freedom from the several failure modes. The definition of PEE can be found in section 11.1 of the study protocol.

To evaluate the primary objective of the study, the 12-month effectiveness success rate will be compared against a PG of 50%. The formal hypotheses to test the primary effectiveness endpoint is given as follows:

$$H_0: P_E \leq 0.5$$

$$H_a: P_E > 0.5$$

where P_E represents the 12-month effectiveness success rate.

III. **Secondary Endpoint:**

A single secondary endpoint for the study is defined as the change in total AFEQT score at 12M post procedure compared to baseline score. The definition of secondary endpoint can be found in section 11.2 of the study protocol.

The change in quality of life 12 months after the ablation procedure assessed by the AFEQT score will be formally tested using the following set of hypotheses:

$$H_0: \mu_d \leq 0$$
$$H_A: \mu_d > 0$$

where μ_d is the mean change of overall AFEQT scores between baseline AFEQT score and 12-month AFEQT score (i.e., $AFEQT_{12M} - AFEQT_{baseline}$).

22.4 Levels of Significance

CCI [redacted]

CCI [redacted]

22.5 Sample Size Justification

CCI [redacted]

22.6 Analysis Sets

Safety Population Analysis Set (SP): CCI [redacted]

Modified Intention-To- Treat (mITT) Analysis Set: CCI [redacted]

Per Protocol (PP) Analysis Set: CCI [redacted]



22.7 Analyses to be Conducted

22.7.1 General Conventions

Descriptive summaries for continuous variables include the number of observations (n), mean, standard deviation (SD), median, 25th percentile (Q1), 75th percentile (Q3), minimum (Min), and maximum (Max). For categorical data, frequency tables will be provided to show the count (n) and percentage (%) within individual a particular category. Percentages will be based on the number of observations with available data.

22.7.2 Disposition and Study Subjects

Disposition and accountability of the study subjects will be summarized descriptively for the subject categories defined in section 13.1.4.

22.7.3 Demographic and Baseline Characteristics

Subject demographics and baseline characteristics such as medical history, history of previously failed AADs, atrial fibrillation history, and concomitant AAD after enrollment will be summarized descriptively for CCI [redacted]

22.7.4 Primary Endpoint Analyses

22.7.4.1 Early Success Interim Analysis

CCI [redacted]

For the Primary Safety Endpoint:

CCI [redacted]

CCI

[redacted]

For the Primary Effectiveness Endpoint:

CCI

[redacted]

CCI [redacted]

[redacted]

22.7.4.2 Final Analysis

CCI [redacted]

For Primary Safety Endpoint:

CCI [redacted]

[redacted]

[redacted]

For Primary Effectiveness Endpoint:

CCI [redacted]

[redacted]

[redacted]

22.7.5 Handling of Missing Data

- CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

22.7.6 Sensitivity Analysis

To ensure the robustness of the primary analysis results, several sensitivity analyses will be conducted for primary endpoints. The specific details of these analyses will be elaborated in the SAP.

22.7.7 Subgroup Analysis

Subgroup analyses by clinically relevant factors CCI [redacted] will be performed and details will be provided in the SAP.

22.7.8 Secondary Endpoint Analysis and Associated Hypothesis

If early success is achieved or both primary endpoints are met at the final primary analysis, then the secondary hypothesis will be tested when all subjects have completed their 12-month follow-up, otherwise descriptive statistics will be presented. If the primary endpoints are met, and the p-value

for the hypothesis test of the secondary endpoint is significant at an alpha level of 2.5%, a claim will be made based on the secondary endpoint analysis result.

For the secondary endpoint analysis, the AFEQT scores assessed at baseline will be compared to the scores for the 12-month follow-up visit to test whether QOL improved 12 months after treatment.

$$H0: \mu_d \leq 0 \text{ vs. } HA: \mu_d > 0,$$

where μ_d is the mean change of overall AFEQT scores between baseline AFEQT score and 12-month AFEQT score (i.e., $AFEQT_{12M} - AFEQT_{baseline}$).

CCI [redacted]

[redacted]

22.7.9 Additional Endpoint Analyses

No formal statistical hypothesis tests will be formulated and performed for the additional endpoints. Descriptive statistics will be provided on all additional endpoints in the analysis sets specified below.

CCI [redacted]

Additional safety endpoints will be analyzed CCI [redacted] analysis sets. Additional effectiveness endpoints will be analyzed CCI [redacted] analysis sets. Procedure data will be summarized in the CCI [redacted] analysis sets. Details of these analyses will be elaborated in the SAP.

23. Ethics and Protection of Human Subjects

23.1 Ethics Review

Study materials including informed consent, survey questionnaires, and any proposed advertising or recruitment materials must be reviewed and approved by an appropriately constituted EC before enrollment of subjects. The Sponsor and the EC must approve in writing any changes to the protocol, informed consent documents, and other study documentation referenced above.

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

23.2 General Duties

Biosense Webster's general duties consist of submitting the clinical investigation application to requisite Health Authorities as warranted , assuring that sites have received EC approval prior to

shipping the devices, selecting investigators, ensuring proper clinical site monitoring and ensuring subject informed consent is obtained.

23.2.1 Data Quality and Reporting

Biosense Webster is responsible for providing quality data that satisfy federal regulations and informing proper authorities of serious unanticipated AEs and deviations from the CIP.

23.2.2 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.

23.2.3 Supplemental Applications

As appropriate, Biosense Webster will submit changes in the Clinical Investigational Plan to the investigators to obtain all applicable re-approvals.

23.2.4 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.

23.2.5 Submitting Reports

Biosense Webster will submit any required regulatory reports identified in this section of the regulation. This may include UADEs, withdrawal of EC approval, current investigators list, annual progress reports, recall information, final reports and CIP deviations.

23.3 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 and regulations of subject Health Authorities and the local government. For this study, MDR2017/745 will be applicable, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. The Sponsor will also maintain compliance with GCP (ICH E6 (R2), 9 November 2016), the European standard EN ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects), the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, Fortaleza 2013), 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 AEs 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 Protocol. 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 Protocol 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 UADEs, withdrawal of EC approval, current investigators list, annual progress reports, recall information, final reports, and Protocol deviations.

23.4 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation.

Discussion of risks and possible benefits of participation will be provided to the subjects as part of the informed consent process. Consent forms will be EC approved and the subjects will be asked to read and review the document. The investigator, or designee, will explain the research study to the subjects and answer any questions that may arise. All subjects will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. The investigator, or designee, will explain that any new information that develops over the course of the study will be provided to the subject in a timely manner. Information should be given to the subjects in a language and at a level of complexity understandable to the subjects in both oral and written form by the principal investigator or designee. Subjects will have ample opportunity to review the written consent form and to ask questions prior to signing.

Prior to participation in the trial, the ICF should be signed and personally dated by the subject or his/her legal representative. If a witness is used for an illiterate subject, the witness should also sign the consent form, attesting that informed consent was freely given by the subject or his/her legal representative. The subject may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subject will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. A signed and dated copy of the ICF must be collected from each enrolled subject and kept in the study subject files and medical records. The site should provide each subject with a copy of their fully executed ICF.

Remote- and e-consenting is permissible with prior approval by Sponsor and in compliance with the site's EC policy.

The Sponsor and the reviewing EC must approve any modifications to the ICF for this clinical investigation. A copy of the EC approved ICF must be maintained by each investigator.
Documentation of the consent process for each subject should be maintained in their medical record by each investigator.

Subjects should not be coerced, persuaded, or unduly influenced to participate or continue to participate in the trial.

23.5 Confidentiality

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

23.6 Subject Confidentiality/Record

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

Site personnel should also be attentive to privacy considerations and should not transmit PHI outside of PI control (e.g., via .pdf scans) without redaction of patient identifiers. Privacy considerations such as above will also be covered in protocol training for both Sponsor representatives and study site personnel.

24. Data Handling and Record Keeping

24.1 Data Collection and Management Responsibility

The Sponsor will be responsible for all data management activities. These activities include development of an 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.

24.1.1 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.

24.1.2 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 system). 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 regulatory authorities, acting in their official capacities, will have access to these confidential files.

24.1.3 Data Reporting

The investigator, or a designated individual, is responsible for ensuring that clinical investigation data are properly recorded on each subject's eCRF and related documents. Completed eCRFs 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 including original (source) records and subject eCRFs by Sponsor representatives and/or responsible government agencies.

It is recommended that all eCRF data be entered by the designated site personnel as soon as possible. It is the responsibility of the investigator to provide timely completion of eCRFs, including procedural data, for review by the Sponsor. For AE reporting, refer to the Adverse Event Reporting Requirements and timelines noted within this clinical protocol.

Investigators are required to prepare and submit accurate and timely reports on this study to the Sponsor and governing EC, if necessary, per Table 15.

Table 15: 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
Clinical Study 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 Should report to ECper local requirements

Upon completion or termination of the Sponsor study, the principal investigator must submit a final written report to the approving Investigational Review Board (as required by the EC) and provide a copy to the Sponsor. The report should contain the information required by the EC and be submitted in the time frame required by the EC.

24.1.4 Data Verification and Review

The Sponsor 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. The sponsor may 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.

24.1.5 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.

24.2 Study Record Retention and Archiving

Records and reports for the study will remain on file at the site for a minimum of 10 years or per country specific record retention requirements following notification by the Sponsor that all investigations have been terminated or completed, or in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market. This documentation must be accessible upon request by the CAs, the Sponsor, or a designee. 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.

24.2.1 Records

Records to be maintained by the investigator include:

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

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

- Signed Patient ICF
- All completed electronic CRFs and supporting source documentation
- Supporting documentation of any AEs and/or death.
- The investigator must retain copies of procedure reports, procedure nursing notes and the results of any interventional procedures that occur while the subject is enrolled in the study. The Sponsor reserves the right to secure data clarification and additional medical documentation on subjects enrolled in this study.

25. Quality Assurance and Quality Control

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 CIP, 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 CAs.

26. Study Suspension or Termination

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

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

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

27. Data and Publication Policy

Publications and/or presentation of clinical investigation results will be coordinated between the Sponsor 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.

As per ISO 14155:2020 paragraph 5.4. a description of this clinical investigation will be registered in publicly accessible database (http://www.ClinicalTrials.gov) and content will be updated throughout the study. Results will be entered at completion of the clinical investigation.

28. Document Filing

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

29. Scientific References

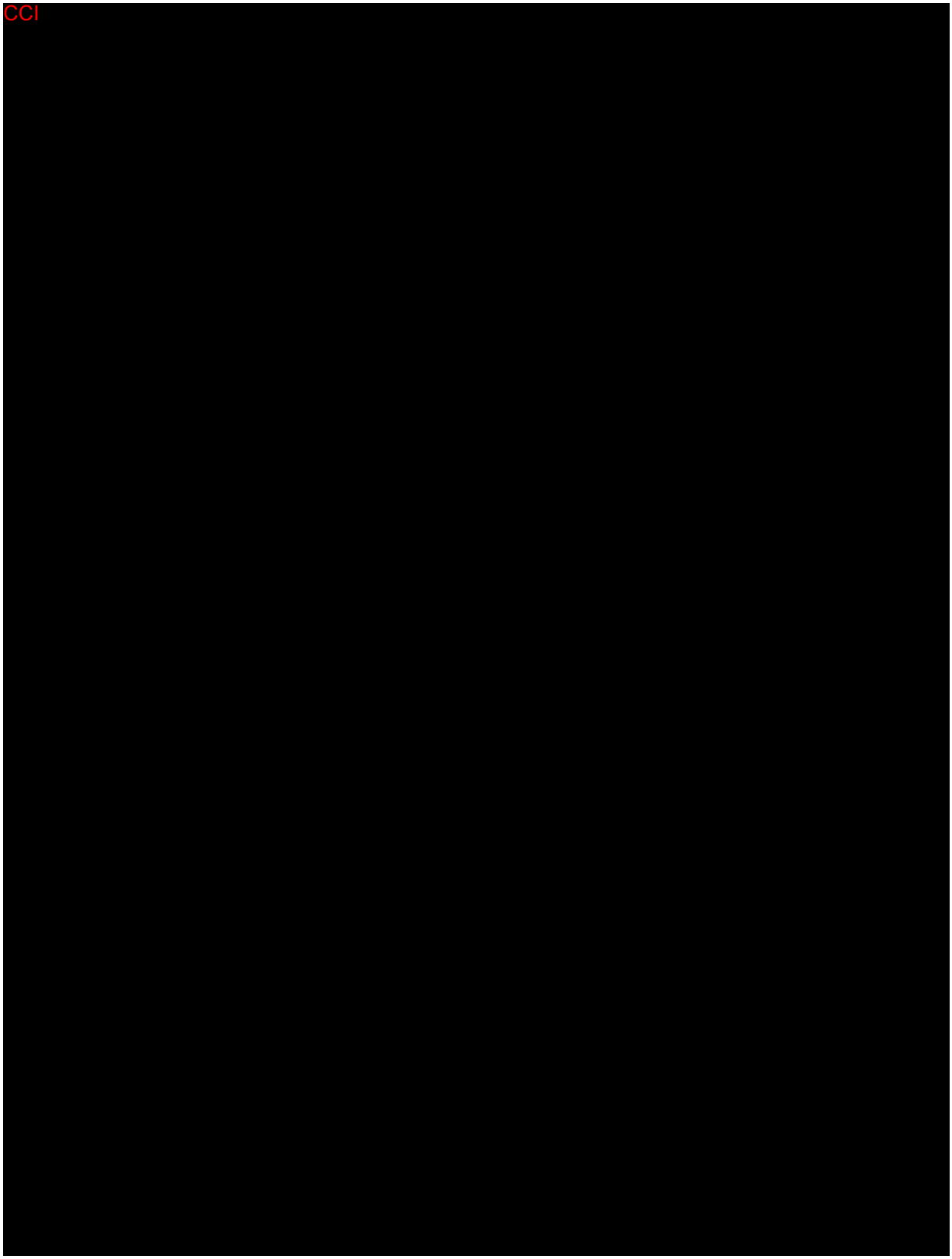
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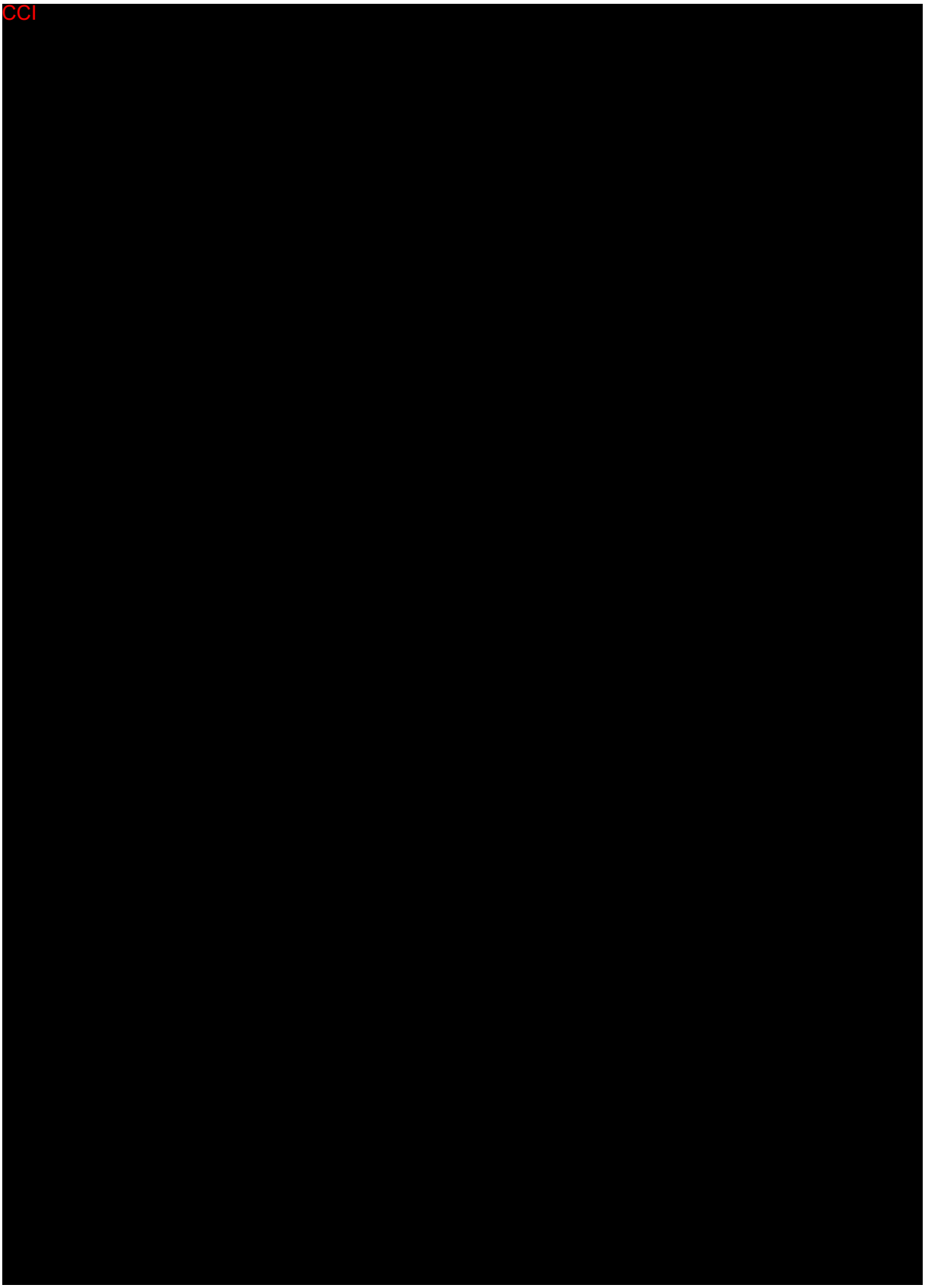
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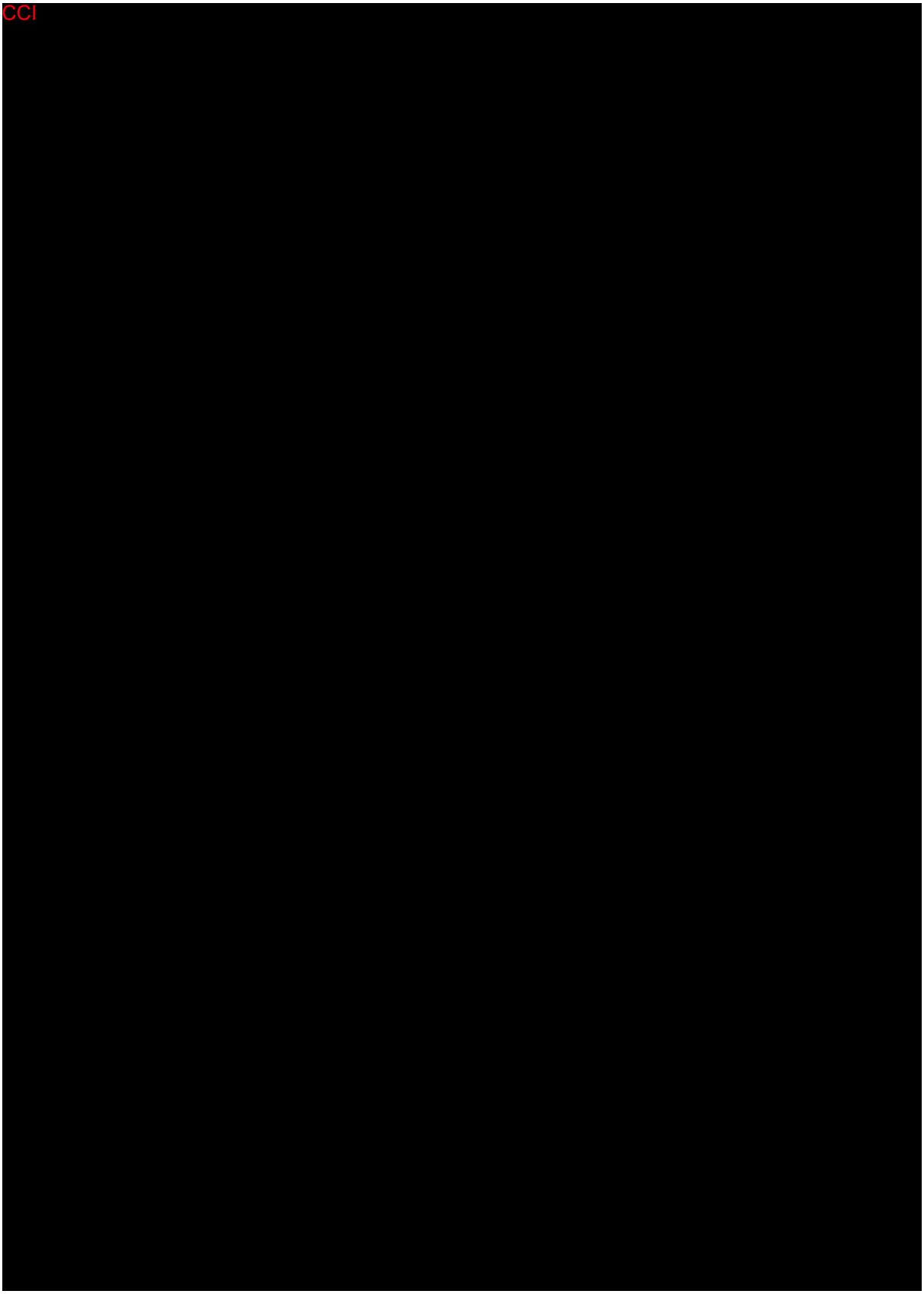
30. Appendix 1 – CCI



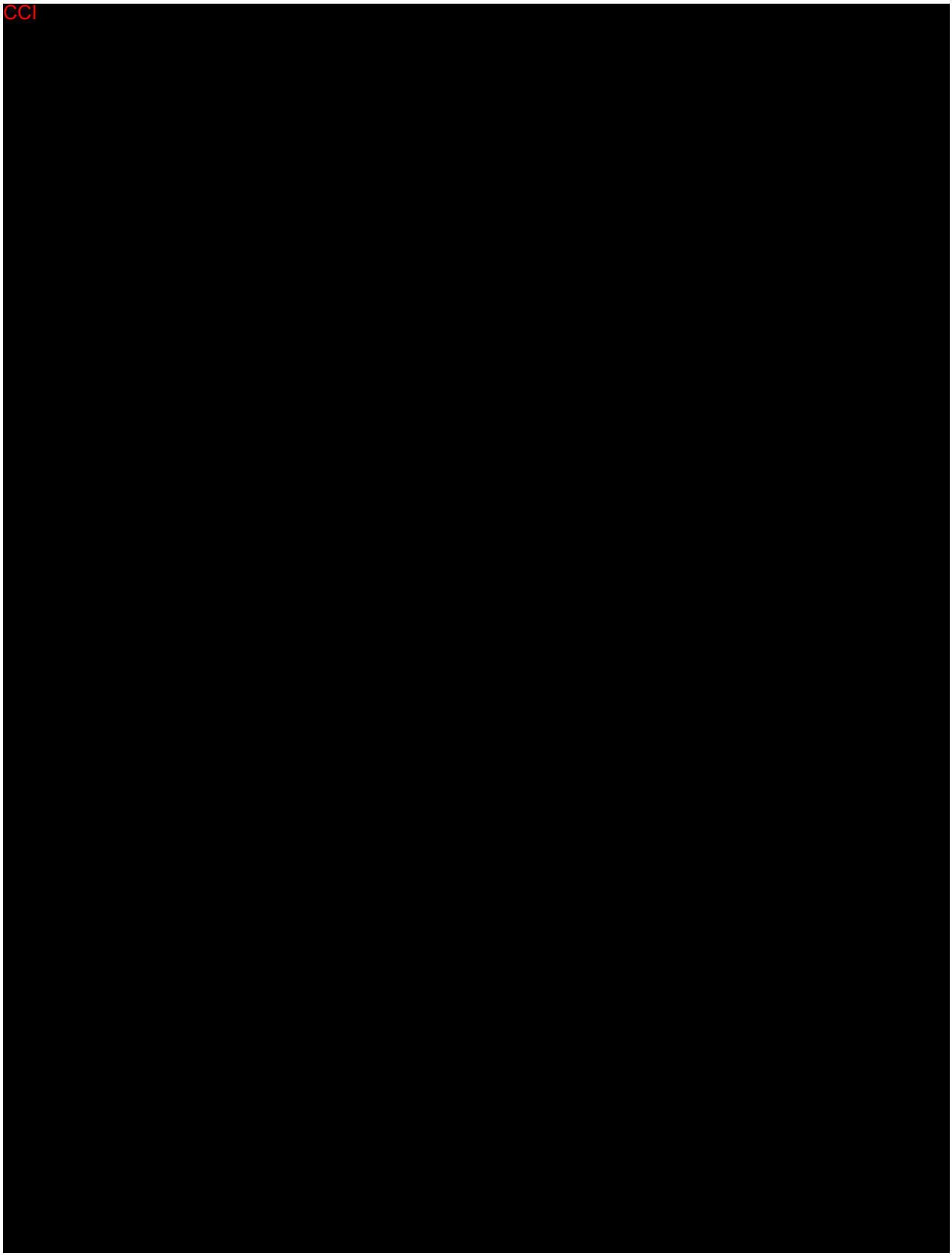
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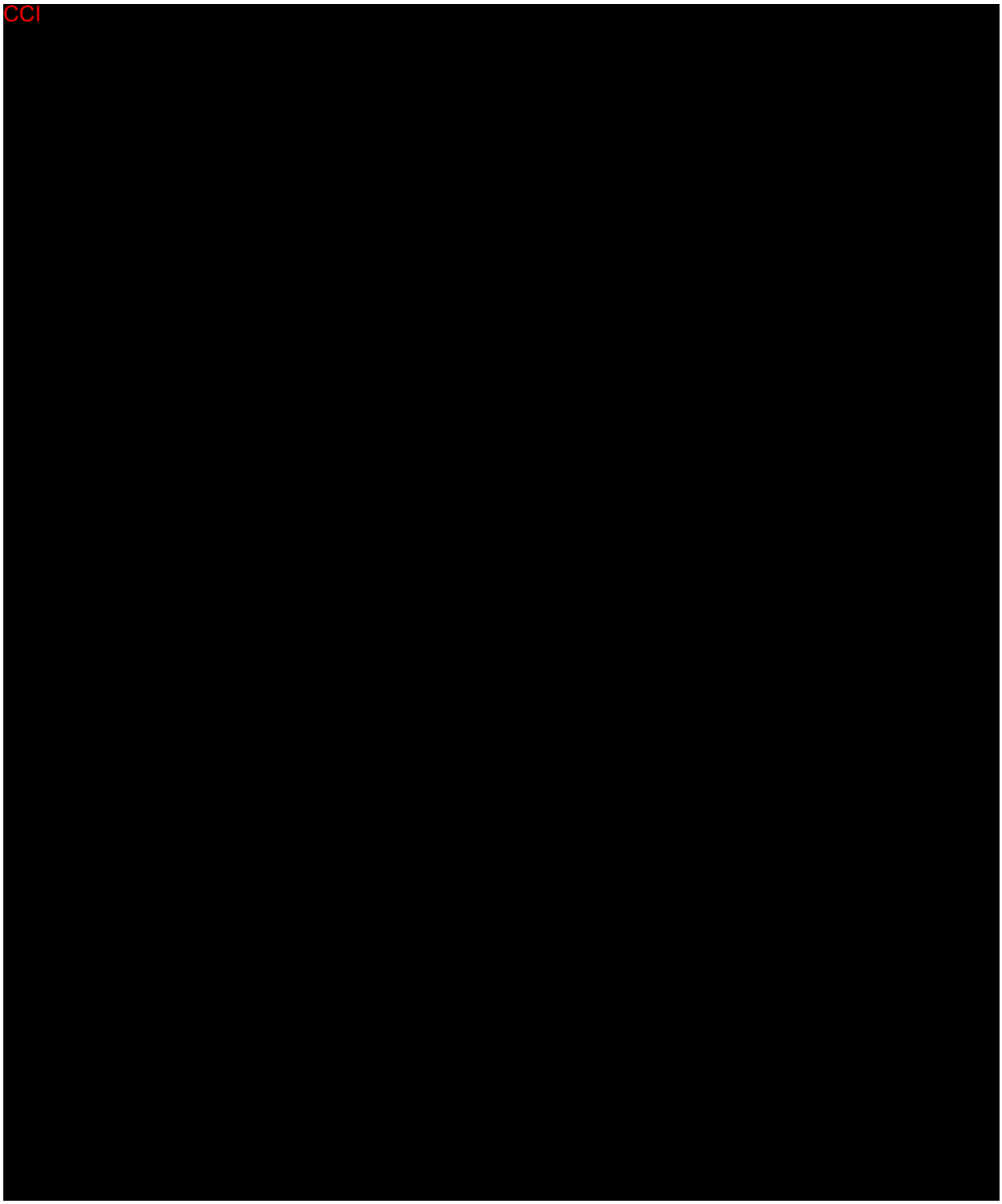


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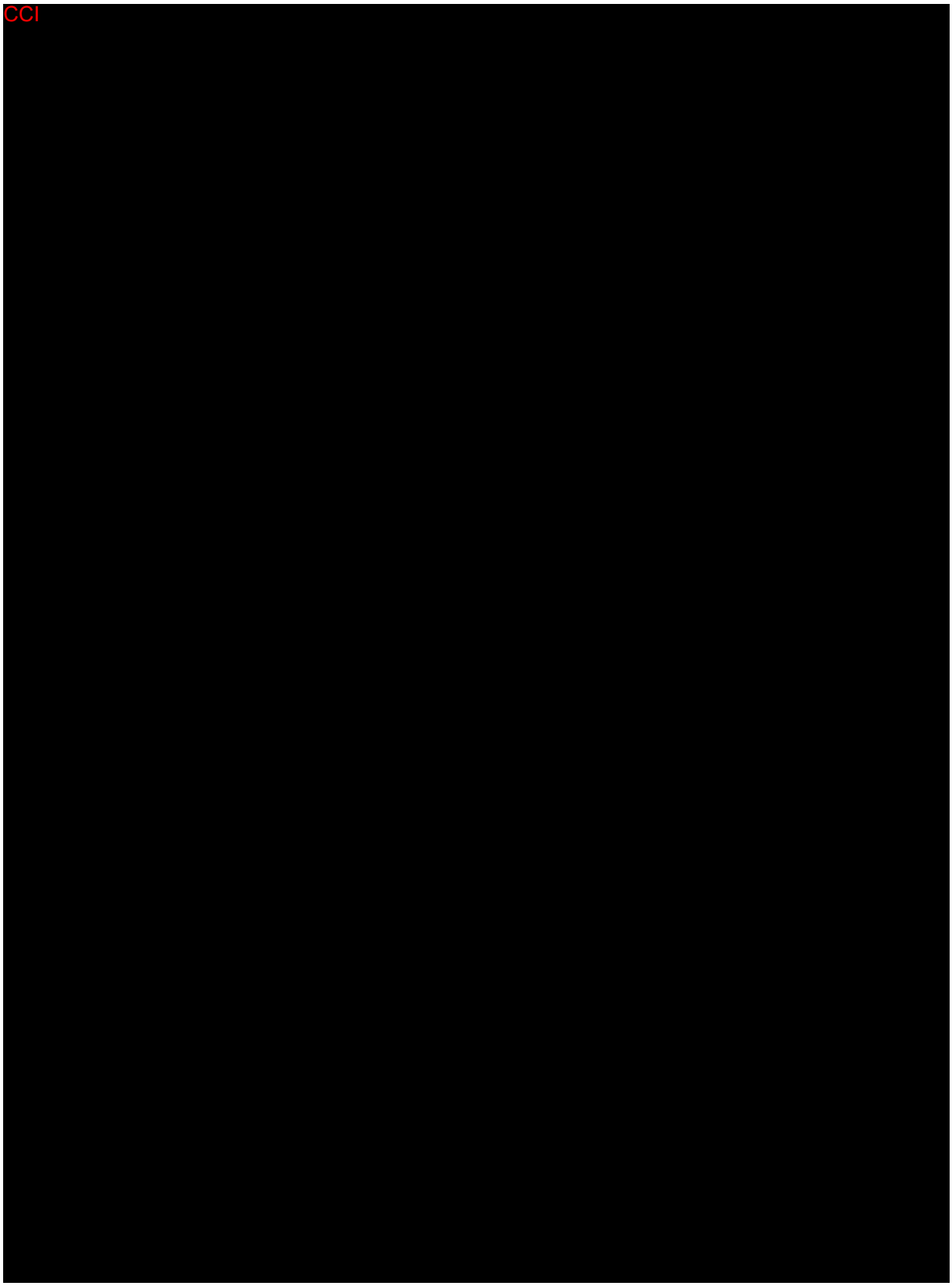


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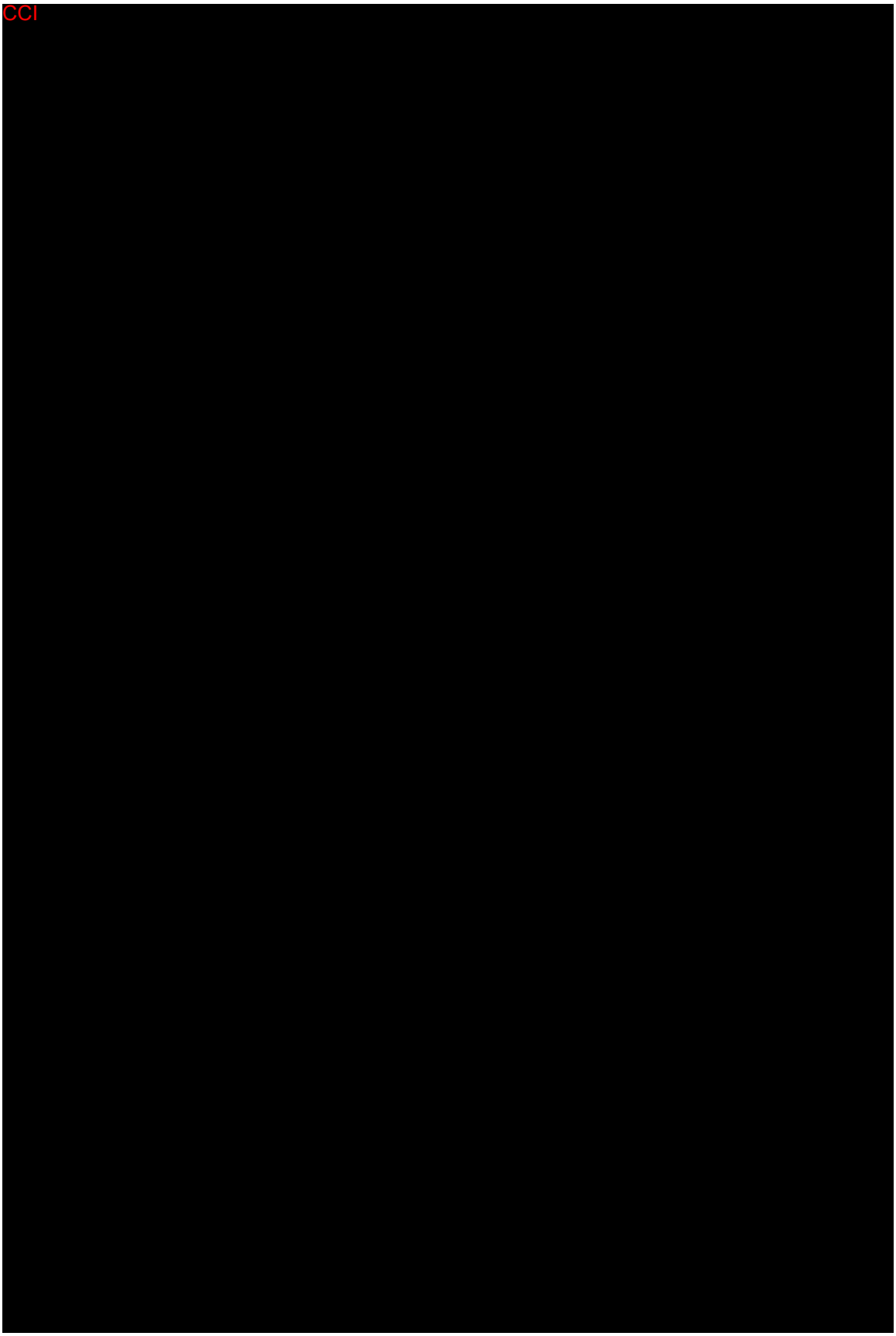



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31. Appendix 2

Summary of previous clinical investigations with similar devices

Name of the previous Clinical Investigation (CI)	NCT#	Manufacturer	Investigational Medical Device (IMD)	Model of IMD	Indication	Target population in the study	Duration of use	Any other important differences between the previous CIs and the current CI
SMART-SF	NCT01385202	Biosense Webster, Inc.	THERMOCOOL SMARTTOUCH™ SF Catheter	D-1348-XX-SI curves DD, FF, JJ, DJ and DF D-1347-XX-SI curves D, F, J	It is indicated for catheter-based cardiac electrophysiological mapping (stimulation and recording) and, when used in conjunction with an RF generator, for cardiac ablation. It provides a real-time measurement of contact force between the catheter tip and heart wall, as well as location information when used with the CARTO™ 3 System.	Adult patients with symptomatic paroxysmal atrial fibrillations	It is non-implanted catheter intended for single-patient, single-use only. There is no specific limitation in duration of use; however, cardiac ablation procedures typically last 2 to 4 hours.	The study was testing the catheter when used in conjunction with an RF generator. It was conducted at 17 US sites.
PRECEPT	NCT02817776	Biosense Webster, Inc.	THERMOCOOL SMARTTOUCH™ SF catheter	D-1348-XX-SI curves DF, FF and FJ D-1347-XX-SI curves D, F, J	It is indicated for catheter-based cardiac electrophysiological mapping (stimulation and recording) and, when used in conjunction with an RF generator, for cardiac ablation. It provides a real-time measurement of contact force between the catheter tip and heart wall, as well as location information when used with the CARTO™ 3 System.	Adult patients with relatively early persistent atrial fibrillations, with episodes lasting >7 days but not more than 1 year.	It is non-implanted catheter intended for single-patient, single-use only. There is no specific limitation in duration of use; however, cardiac ablation procedures typically last 2 to 4 hours.	The study was testing the catheter when used in conjunction with an RF generator. It was conducted at 30 sites in US and Canada with total enrolment of 381 subjects. The PRECEPT study used both a 3-month "medication adjustment period" and an additional 3-month "therapy consolidation" period, creating a 6-month "blanking period" during which: 1) additional ablations could be performed; and/or 2) antiarrhythmic medications could be added or adjusted.
VISTAX	NCT03062046	Biosense Webster, Inc.	Ablation Index and VISITAG™ software in combination with a THERMOCOOL SMARTTOUCH™ (ST) or SmartTouch Surroundflow™ (STSF) catheter	Ablation Index module V4 was investigational, STSF not investigational and could be used from the shelf	During RF application, when the VISITAG™ filter thresholds are met, the Tag Index value appears on the Readings Dashboard.	Adult patients with symptomatic paroxysmal atrial fibrillations	Ablation Index and VISITAG™ software is installed in The CARTO™ 3 System, which is a multiple-use medical device provided non-sterile, and as such it has no	This study was conducted to evaluate safety and effectiveness of a standardized RF ablation workflow.

Name of the previous Clinical Investigation (CI)	NCT#	Manufacturer	Investigational Medical Device (IMD)	Model of IMD	Indication	Target population in the study	Duration of use	Any other important differences between the previous CIs and the current CI
							therapeutic use lifetime.	
SURPOINT	NCT03624881	Biosense Webster, Inc.	VISITAG SURPOINT Module with External Processing Unit (EPU) in combination with THERMOCOOL SMARTTOUCH™ SF (STSF) and THERMOCOOL SMARTTOUCH™ (ST) catheters	D-1348-XX-S curves DF, FF, and FJ; D-1347-XX-S	During RF application, when the VISITAG™ filter thresholds are met, the Tag Index value appears on the Readings Dashboard.	Adult patients with drug-resistant symptomatic atrial fibrillations (paroxysmal or persistent)	The VISITAG SURPOINT Module of the CARTO™ 3 System is a multiple-use medical device provided non-sterile, and as such it has no therapeutic use lifetime.	This study was conducted to evaluate the application during RF ablation.
InspIRE	NCT04524364	Biosense Webster, Inc.	TRUPULSE™ GeneratorVARIPULSE™ Bi-Directional Catheter	D-1417-01-I (TRUPULSE™ Generator) D-1412-01-SI (VARIPULSE™ Bi-Directional Catheter)	The VARIPULSE™ Catheter is indicated for use in catheter based cardiac electrophysiological mapping (stimulating and recording) and, when used with a TRUPULSE™ Generator, for cardiac ablation. The catheter provides location information when used with the CARTO™ 3 System.TRUPULSE™ Generator is indicated for use in conjunction with compatible cardiac ablation catheters to deliver pulsed field (PF) and radiofrequency (RF) energy during cardiac ablation procedures.	Adult patients with symptomatic paroxysmal atrial fibrillation	The VARIPULSE™ Catheter is non-implanted sterile catheter intended for single-patient, single-use only. There is no specific limitation in duration of use. The therapeutic device lifetime is the length of the procedure. Traditional point-by-point cardiac RF ablation typically last 2 to 4 hours.The TRUPULSE™ Generator s a reusable non-patient contacting device. There is no specific limitation in	This study consists of two sequential waves. The WAVE I was the safety characterization phase, with intention to delineate safety and provide preliminary estimates for safety and acute effectiveness of the IRE system. The WAVE II phase was to evaluate safety and long-term effectiveness.

Name of the previous Clinical Investigation (CI)	NCT#	Manufacturer	Investigational Medical Device (IMD)	Model of IMD	Indication	Target population in the study	Duration of use	Any other important differences between the previous CIs and the current CI
							duration of use. The therapeutic device lifetime is the length of the procedure.	
AdmIRE	NCT05293639	Biosense Webster, Inc.	TRUPULSE™ Generator VARIPULSE™ Bi-Directional Catheter	D-1417-01-I (TRUPULSE™ Generator) D-1412-01-SI (VARIPULSE™ Bi-Directional Catheter)	The VARIPULSE™ Catheter is indicated for use in catheter based cardiac electrophysiological mapping (stimulating and recording) and, when used with a TRUPULSE™ Generator, for cardiac ablation. The catheter provides location information when used with the CARTO™ 3 System. TRUPULSE™ Generator is indicated for use in conjunction with compatible cardiac ablation catheters to deliver pulsed field (PF) and radiofrequency (RF) energy during cardiac ablation procedures.	Adult patients with symptomatic paroxysmal atrial fibrillations	The VARIPULSE™ Catheter is non-implanted sterile catheter intended for single-patient, single-use only. There is no specific limitation in duration of use. The therapeutic device lifetime is the length of the procedure. Traditional point-by-point cardiac RF ablation typically last 2 to 4 hours. The TRUPULSE™ Generator s a reusable non-patient contacting device. There is no specific limitation in duration of use. The therapeutic device	The study was conducted at 30 US sites with the total enrollment of 362 subjects.

Name of the previous Clinical Investigation (CI)	NCT#	Manufacturer	Investigational Medical Device (IMD)	Model of IMD	Indication	Target population in the study	Duration of use	Any other important differences between the previous CIs and the current CI
							lifetime is the length of the procedure.	

32. Appendix 3

Comprehensive List of Anticipated Adverse Events

Anticipated Adverse Events	
(Acute) renal failure	Infection, systemic
(Aspiration) pneumonia	Inflammation
(Skin) laceration	Isolated ST segment elevation
(Vascular) bleeding	Liver toxicity
Acute Respiratory Distress Syndrome (ARDS)	Local Hematoma/ecchymosis
Air embolism	Localized skin reaction
Allergic reaction to contrast media	Mitral Insufficiency
Allergic skin reaction	Myocardial infarction with or without ST elevation
Altered Mental Status Confusion; Altered Level of Consciousness;	Nausea
Anaphylactic shock	Neurological disorders (poor coordination)
Anemia	Neurological disorders (tremor)
Anesthesia complications/reactions	Neuropraxia/Muscle contraction
Anoxic or hypoxic encephalopathy	Palpitations
Aortic Puncture	Papillary Muscle tear/injury
Apnea - sedation induced	Pericardial effusion resulting in tamponade
Arrhythmia (new or worsening of pre-existing arrhythmia)	Pericardial effusion without tamponade
Asthmatic attack	Pericarditis
Asymptomatic Cerebral Emboli	Periesophageal vagal nerve injury
Atelectasis	Peripheral nerve injury
Atrial fibrillation	Phlebitis
Atrial Septal Defect (acquired)	Phrenic nerve damage/injury
Atrio-Esophageal fistula	Pleural effusion
Auditory Disorder	Pneumothorax
AV fistula	Post- and perioperative pain
Back Pain	Post Procedural Hematuria
Bone disorder	Pseudoaneurysm
Bronchial fistula, Broncho-pericardium fistula	Pulmonary edema
Cardiac arrest	Pulmonary embolism
Cardiac pacemaker insertion or replacement	Pulmonary hypertension
Cardiac perforation	Pulmonary toxicity, like acute pulmonary syndrome
Cardiac Valve Rupture/Damage	Pulmonary vein dissection
Cardiogenic Shock	Pulmonary vein stenosis
Cerebro-Vascular accident (CVA)/Stroke	Renal Artery Stenosis
Chest pain/discomfort	Respiratory arrest
Complete or incomplete heart block	Respiratory depression
Conduction block	Respiratory failure
Coronary Artery Stenosis	Respiratory infection

Anticipated Adverse Events	
Coronary artery thrombosis	Retinal Artery Embolism
Death	Retroperitoneal bleeding
Deep venous thrombosis	Rhabdomyolysis, including produced by body position or propofol
Diaphragmatic paralysis	Sedation induced CO_2 retention with lethargy and cholecystitis
Dislodgement/Malfunction of pacemaker/defibrillator leads	Seizure
Disseminated Intravascular Coagulation	Sepsis
Dizziness, presyncope, vertigo	Sinus bradycardia
Dysphagia	Sinus tachycardia
Dyspnea	Skin burn or necrosis
Endocarditis	Skin discoloration
Epigastric Distress	Skin edema
Epistaxis	Skin or soft tissue (radiation) injury/tear
Esophageal injury / perforation	Subclavian artery puncture
Expressive aphasia	Temperature elevation / Fever
Fatigue	Thrombocytopenia
Gastric hypomotility	Thromboembolism
Gastroesophageal reflux	Thrombosis
Gastrointestinal disorders	Thyroid disorders
Gastrointestinal diverticulosis	Toxic reaction
Gastroparesis	Transient extremity numbness
Headache	Transient Ischemic attack (TIA)
Heart failure (acute or chronic)	Urinary Retention Postoperative
Heart injury	Urinary tract injury or infection related to the urinary catheter
Heart valve insufficiency	Valvular damage/insufficiency
Hemoptysis	Vascular (access) dissection (including coronary arteries)
Hemorrhage	Vascular occlusion
Hemothorax	Vasovagal reactions
High/increased creatine phosphokinase (CPK)	Ventricular Fibrillation
Hypertension	Vessel damage/trauma
Hypervolemia	Vessel perforation
Hypotension	Vessel spasm (including coronary arteries)
Hypovolemia	Visual disturbance
Hypoxia	Worsening of pre-existing pulmonary disease
Increased phosphokinase level	Wound healing disturbance
Infection, localized	

*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.