The Effectiveness and Safety in the treatment of CPVI for Symptomatic Paroxysmal Atrial Fibrillation with THERMOCOOL® SMARTTOUCH™ Catheter in China——A Multi-center Clinical Registry Study

Statistical analysis plan

Fountain Medical Development Co., Ltd
May 19, 2016

Statistical analysis plan

Title:	The Effectiveness and Safety in the treatment of CPVI for Symptomatic Paroxysmal Atrial Fibrillation with THERMOCOOL® SMARTTOUCH™ Catheter in China——A Multi-center Clinical Registry Study (SMART CHINA)
Product name	THERMOCOOL® SMARTTOUCH™ Catheter
Study No.	BW-201501
Study device name:	THERMOCOOL® SMARTTOUCH™ Catheter
Study method:	This is a prospective, multicenter, non-randomized clinical study to make clinical evaluation for THERMOCOOL® SMARTTOUCH™ catheter undergoing CPVI by comparing with an objective performance goal. 200 (at least 188) subjects are planned to be enrolled from at most 15 study sites in China.
Sponsor:	Johnson & Johnson Medical (Shanghai) Ltd.
Principal investigator:	Dr.Huang Congxin
Statistical analysis	The purpose of this study is to assess the effectiveness and safety of the THERMOCOOL® SMARTTOUCH™ catheter in the treatment of drug refractory symptomatic paroxysmal atrial fibrillation undergoing CPVI. Assuming the true rate for freedom from documented symptomatic AF, AT, or AFL episodes through 12-months follow-up is about 65% with CF-guided approach and a historic control performance goal of 50%, [12] a sample size of 150 is needed in order to have 95% power to have the lower bound of the two-sided 95% confidence interval of this recurrence free rate above the historic control performance goal. This sample size is computed using nQuery Advisor® version 7.0. Considering 20% dropout rate, a sample size of 188 is needed. This study will enroll approximately 200 subjects (no less than 188). Statistical methods applied will be mostly descriptive statistics, which will be calculated in statistical report form. For continuous variables, the number of cases, mean values, medians, standard deviations, Q1, Q3 and maximum and minimum values will be calculated. For categorical variables, the number of cases and percentages will be calculated. Statistical testing will be carried out at the two-sided α=0.05 level unless

otherwise specified; 2-sided 95% confidence intervals will be presented, where specified.

Primary efficacy endpoint:

The primary effectiveness endpoint for this study will be freedom from documented symptomatic AF, AT, or AFL episodes through 12-months follow-up after the index ablation procedure (includes a three month blanking period). The number of subjects who achieved this endpoint and its percentage will be presented. A two-sided binomial exact 95% confidence interval will be computed. Superiority against historic control performance goal (50%) after applying THERMOCOOL® SMARTTOUCH™ catheter with contact sensing will be claimed if the lower bound of this confidence interval is above 50%.

A Kaplan-Meier analysis will be performed for the time to the first documented symptomatic AF, AT, or AFL episode. The first quartile, median, and third quartile and 95% confidence intervals of the first quartile, median and third quartile will be computed.

Baseline covariates and procedure parameters that affect the occurrence of the first AF, AT, or AFL episode will be explored using logistic regression models.

Secondary efficacy endpoints:

For acute success rate at 0.5h post CPVI, the number of subjects who achieved this endpoint and its percentage will be presented. A two-sided binomial exact 95% confidence interval will be computed.

For CF and Force Time Integral for index procedure by PV segments, descriptive summary statistics and the 95% two-sided asymptotic confidence intervals will be presented.

For PV reconnections after the index procedure, descriptive summary statistics will be presented. Frequency counts and percentages will be used to summarize the sites of PV reconnection. A two-sided binomial exact 95% confidence interval will be computed. Proportion of PV reconnections will be computed for each subject. And then the descriptive summary statistics and 95% two-sided asymptotic confidence intervals will be used to summarize the proportion of PV reconnection across subjects.

For total procedural, ablation time and fluoroscopy time, descriptive summary statistics and 95% two-sided asymptotic confidence intervals will be presented.

Correlation between the secondary efficacy endpoints and the primary efficacy endpoint will be explored with appropriate statistical methods (such as regression analysis or correlation coefficient and so on).

Safety endpoint:

The incidence of AEs related with the procedure and study catheter.

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Signature Page

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Study No.: BW-201501

Sponsor: JJMS

Prepared by:
Redacted

Reviewed by:
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Table of Contents

Acronym/Abbreviation

Acronym/Abbreviation	Expanded Term
AAD	Antiarrhythmic Drug
AE	Adverse Event
AF	Atrial Fibrillation
AFL	Atrial flutter
AT	Atrial Tachycardia
ATC	Anatomical Therapeutic Chemical classification
CRF	Case Report Form
ECG	Electrocardiogram
HM	Holter Monitoring
HRS/EHRA/ECAS	Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society
ITT	Intent-to-treat analysis set
LA	Left Atrium
PAF	Paroxysmal atrial fibrillation
PP	Per protocol set
PT	Preferred term
PVI	Pulmonary Vein Isolation
RA	Right atrium
RF	Radiofrequency
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SOC	System organ classification
SS	Safety analysis set
TEAE	Treatment emergent adverse events
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography

The statistical analysis plan (SAP) provides descriptive statistical analysis method and data processing principle, analyzes and reports the effectiveness and safety of the study. The preparation of the statistical analysis plan is based on BW-201501 clinical study protocol (January 7, 2016).

1 Project introduction

1.1 Background

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1.2 Rationale

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1.3 Device Description

The commercially available THERMOCOOL® SMARTTOUCH™ catheter Diagnostic /Ablation Deflectable Tip Catheter with Contact Force Sensing Capability is the only study catheter to be used in this study.

The catheter is a multi-electrode luminal catheter with a deflectable 3.5 mm tip designed to facilitate electrophysiological mapping of the heart and to transmit RF current to the catheter tip electrode for ablation purposes. The catheter shaft measures 7.5 F with 8.0 F ring electrodes. For ablation, the catheter is used in conjunction with an RF generator and back electrodes.

The catheter has force sensing technology that provides a real-time measurement of contact force between the catheter tip and the beating heart wall. It is specifically designed to allow full integration with the electro-anatomic mapping system, which provides both graphical and numerical displays of CF and the force vector in real time; thus both magnitude and direction of the force are visualized via a 3-D vector. This catheter is a modification of the widely used bidirectional diagnostic/ablation catheter (THERMOCOOL® EZ Steer™, Biosense Webster) and unidirectional NAVISTAR diagnostic/ablation l catheter (NAVISTAR THERMOCOOL®, Biosense Webster), using a similar irrigation and bidirectional/ unidirectional system. Only the distal tip has been modified with additional elements to accomplish CF sensing.

The VisiTag™ Module software applies a novel algorithm which could automatically tags multiple ablation parameters and present them on the Carto® 3 Mapping System. It can ensure recording of multiple intra-cardiac electrograms and signals from the RF generator (i.e., power, temperature, impedance) at the same time of RF discharge.

Study participants who undergo PVI are to have their procedure performed and completed (as described in section 5.4) using the study device in conjunction with the CARTO® 3 System (version 3.2 or higher), an electro-anatomic mapping system for use in performing catheter-based electrophysiological RF ablation procedures. All devices to be used in this study are commercially available, conform to the applicable local regulations and are to be used according to the approved indication and their Instructions for Use (IFU). Each site will be required to have specific equipment for performing RF ablation procedures. Sites will be instructed to refer to the User's Manual/Instructions for Use for the set-up of system / device / component.

1.4 Risk analysis

RF catheter ablation has been used for about two decades. The use of saline-irrigated ablation catheter is routine for many PAF ablation procedures whose risks and complications are well understood.

1.4.1 Description of Risk Analysis

The incremental risk associated with performing RF catheter ablation using the THERMOCOOL® SMARTTOUCH™ catheter, which includes contact force sensing technology, is small relative to that of a standard electrode catheter that does not include this technology. The larger RF lesion size produced with this catheter may increase pain (during the procedure) associated with RF applications and may increase the risk of cardiac rupture. Increased pain, however, can be managed with intravenous analgesics. Additionally, use of the force sensing catheter may reduce procedural time, fluoroscopy time and increase procedural success by increasing lesion depth and by minimizing thrombus formation, which necessitates repeated removal and re-deployment of the ablation catheter. The ability to cool the electrode-tissue interface allows the use of higher power than with a conventional 4 mm electrode. For any given power setting, the power delivered to the tissue is similar to that used with a 4 mm electrode.

Radiofrequency current may cause occlusion of a coronary artery, either by direct thermal damage, spasm, or thrombosis. Experience at numerous centers suggests that the risk of coronary occlusion is less than 0.5%.[35, 36] Coronary artery occlusion could produce myocardial infarction (MI), angina or death. If occlusion of a coronary artery occur for any reason, the investigator will attempt to restore coronary blood flow through pharmacological, catheter and/or surgical intervention, as medically indicated.

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

A thrombus may form on the ablation electrode during the application of radiofrequency current without any change in impedance. The thrombus might become dislodged and embolize to produce a stroke, MI, or other ischemic injury. The risk of an embolus is reduced by quickly terminating the application of current after an impedance rise, which limits the size of the thrombus on the electrode. Probably the most important aspect of the THERMOCOOL® family of catheters is the near absence or very low likelihood of thrombus formation during RF.

Thrombus formation may produce an arterial or pulmonary embolus. This risk may be reduced by the use of aspirin (antithrombotic) and/or anticoagulation therapy, at the discretion of the investigator.

Cardiac perforation may result from catheter manipulation or application of radiofrequency current (risk is <1%).[35, 36] This may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. Significant hemodynamic compromise can result in neurologic injury or death. An increased risk of cardiac perforation may be associated with the

use of a saline-irrigated electrode catheter due to its ability to create a larger, deeper RF lesion. This risk is greatest in a thin walled chamber (i.e., RA, LA, or RV); however, the risk of perforation related to a deep steam pop is reduced if RF energy is not delivered perpendicular to the wall at power above 35 or 40 watts. If the lesion is deeper, the risk of steam pop is higher above 35-40 watts.

Injury to a cardiac valve may result from catheter manipulation or the application of radiofrequency current (risk <1%).[35-37] This may produce valvular insufficiency and possibly necessitate valve replacement surgery.

The application of RF current along the posterior left atrium can result in thermal injury to the esophagus and the formation of an atrio-esophageal fistula. This is a very rare (0.04%) but severe complication of RF ablation that may require surgical intervention or result in permanent impairment.[37] Reducing power at sites in close proximity to and/or avoiding sites directly over the esophagus may reduce the risk of thermal injury.

Injury to the phrenic nerve may occur as a result of RF application in the region of the right pulmonary veins. The reported incidence of phrenic nerve injury varies from 0% to 0.48%. [37] Prior to ablation in the region of the RSPV, investigators are advised to perform precautionary measures, such as evaluation of proximity to the phrenic nerve and pacing maneuvers.

Radiation exposure during fluoroscopic imaging of 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%).[38-40]

The risk of pulmonary AEs (e.g., pulmonary vein stenosis, thrombus and hypertension), associated with an AF ablation procedure targeting the pulmonary veins, is considered small (<4%).[23, 41-47]

Other potential complications, which may result from catheter insertion and manipulation as part of the prerequisite electrophysiology study and mapping procedure, include: Allergic reaction to the local anesthetic, sedatives, contrast media, heparin, protamine, or other agents administered during the procedure (risk <1%).[48-52] Arterial or venous injury, including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other sites along the vessels (risk <1%),[35,36] which may produce hemorrhage, hematoma or ischemic injury to an extremity or major organ. Hemorrhage as a result of anticoagulation (risk <0.5%), which may require transfusion.[35, 36] Infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%); [35-37] this risk can be minimized by using standard aseptic technique and by the use of antibiotic agents when indicated.

1.4.2 Minimization of Risks

The criteria for subject inclusion, methods, personnel, facilities, and training that have been specified for this study are intended to minimize the risk to subjects undergoing this procedure. Subjects will be screened carefully prior to enrollment in the study to confirm compliance with the study inclusion and exclusion criteria.

Participating investigators should be experienced and skilled in performing electrophysiology examinations, intracardiac mapping, and ablation of AF with the use of the RF ablation catheters. Before study initiation, they will perform CF-guided ablation in 5 patients to become familiar with CF monitoring to decrease learning curve-associated bias. Procedures will be performed in electrophysiology laboratories, with the assistance of skilled nurses and technicians. The laboratory will contain sufficient resuscitative equipment and facilities to manage any potential complication. Cardiac surgical facilities, as well as a qualified cardiovascular surgeon, will be available during the ablation procedure in the event that surgical intervention becomes necessary.

Ablation procedures with the THERMOCOOL® SMATTOUCH™ catheter will be performed according to the product Instructions for Use, including but not limited to instructions regarding indications and contraindications for using these devices.

1.4.3 Precautions

Invasive electrophysiological evaluation and catheter ablation may impart some degree of risk to the patient. The risk of serious complications is generally related to the severity of cardiac disease. The degree of risk of the electrophysiological and catheter ablation procedures and the potential benefit of the treatment of symptomatic PAF should be determined by a qualified physician. Failure to observe all contraindications, warnings, and precautions, as listed in the Instructions for Use may result in procedural complications. Procedural complications include: cardiovascular injury or perforation with or without cardiac tamponade, pericardial effusion, esophageal fistula, severe PV stenosis, pulmonary embolus, tricuspid regurgitation, MI, bleeding at the catheter insertion site, sepsis, stroke, and death.

1.4.4 Potential Benefit

The direct benefit for patients undergoing radiofrequency catheter ablation are elimination of AF episodes, improvement in quality of life, and less frequent hospitalization. The information gathered during the conduction of this study may be of benefit in the future for the treatment of patients with atrial fibrillation.

2 Study Objective

The purpose of this study is to assess the effectiveness and safety in the treatment for drug refractory symptomatic paroxysmal atrial fibrillation (PAF) subjects with the THERMOCOOL® SMARTTOUCH™ catheter undergoing CPVI.

3 Study Design

This is a prospective, multicenter, non-randomized clinical evaluation utilizing the THERMOCOOL® SMARTTOUCH™ catheter undergoing CPVI compared to a pre-determined performance goal. Approximately 200 subjects (minimum 188) will be enrolled at up to 15 sites in the China.

3.1 Screening

All patients considered for a RF ablation procedure for drug refractory recurrent symptomatic PAF should be screened by the investigator or designated member of the research team for study eligibility.

Symptomatic Episode: symptom(s) which is/are concurrent with a documented episode of AF by either Electrocardiogram (ECG), Holter monitor (HM), or transtelephonic monitor (TTM). Symptoms may include but are not limited to: palpitations, irregular pulse (e.g., tachycardia or bradycardia), dizziness, weakness, chest discomfort, and breathlessness.

3.2 Informed Consent Form (ICF)

Informed consent is mandatory and the informed consent form signed and dated by both investigator and subject must be obtained from all subjects prior to CRF entering in this study. Any modifications to the Patient Informed Consent Form must be approved by JJMS and the IEC. The copy of Informed Consent Form approved by IEC along with the copies of consent forms signed by every subject must be maintained by every investigator in a designated clinical trial master file. A signed copy of the consent form must be given to each subject. It is the investigator's responsibility to ensure that the Informed Consent process is performed in accordance with GCP.

3.3 Number of Centers

Up to 15 sites in China will participate in this study. Total enrollment among all sites of up to 200 subjects is expected. Sites participating in this study will be selected based upon their capabilities to successfully carry out those assessments.

CPVI will be performed by experienced operators who have prior experience with the NAVISTAR® THERMOCOOL® and/or EZ STEER® THERMOCOOL® NAV catheters (>50

AF ablation case per year). Before study initiation, operators will be trained on the use of the CF-guided ablation catheter and CARTO®3 VisiTag module for at least 5 patients. Investigators will set personal operating reference ranges using experience gained from this training and the information of the prior clinical (human) studies and published literature. These patients will not be included in the study.

3.4 Subject Selection - Inclusion Criteria

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

1. Aged 18 years or older.

2. Failure of at least one antiarrhythmic drug (AAD) for AF (class I or III, or AV nodal blocking agents such as beta blockers and calcium channel blockers) as evidenced by recurrent symptomatic AF, or intolerance to the AAD

3. Patients with paroxysmal AF eligible for catheter ablation

4. Patients with symptomatic PAF who have had at least one documented AF episode in the twelve (12) months prior to enrollment. Documentation may include but is not limited to electrocardiogram (ECG), Holter monitor (HM) or transtelephonic monitor (TTM)

5. Able and willing to comply with all pre-, post- and follow-up testing and requirements

6. Be able to sign IRB/EC-approved informed consent form

3.5 Subject Selection - Exclusion Criteria

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

1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause

2. Previous surgical or catheter ablation for AF

3. Any PCI, cardiac surgery, or valvular cardiac surgical or percutaneous procedure (e.g., ventriculotomy, atriotomy, and valve repart or replacement and presence of a prosthetic valve) within the past 2 months.

4. Any carotid stenting or endarterectomy.

5. Coronary artery bypass graft (CABG) procedure within the last 180 days (6 months)

6. AF episodes lasting longer than 7 days or terminated via cardioversion

7. Documented left atrial thrombus on imaging

8. Uncontrolled heart Failure or New York Heart Association (NYHA) class III or IV

9. Myocardial Infarction within the previous 60 days (2 months)

10. Documented thromboembolic event (including TIA) within the past 12 months

11. Rheumatic heart disease

12. Awaiting cardiac transplantation or other cardiac surgery within the next 365 days (12 months)

13. Significant pulmonary disease, (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces chronic symptoms.

14. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study

15. Active illness or active systemic infection or sepsis

16. Diagnosed atrial myxoma

17. Unstable angina within the past 60 days (2 months)

18. History of blood clotting or bleeding abnormalities

19. Life expectancy less than 365 days (12 months)

20. Hypertrophic obstructive cardiomyopathy

21. Presence of implanted ICD

22. Contraindication to anticoagulation

23. Contraindication to isoproterenol

24. Presence of intramural thrombus, tumor or other abnormality that precludes catheter introduction or manipulation

25. Presence of a condition that precludes vascular access.

26. Women who are pregnant and/or breast feeding

27. Patients presenting contraindications for study catheter(s), as indicated in the respective Instructions For Use

28. Enrollment in an investigational study evaluating another device, biologic, or drug.

3.6 Subject Disposition

- **Enrolled Subjects**: patients who sign the informed consent.

- **Excluded Subjects**: subjects that are enrolled but never undergo insertion of the Study Catheter. Excluded subjects will not be evaluated in this study.

- **Discontinued Subjects**: subjects that have the investigational catheter inserted but are not treated with the investigational device (i.e., no RF energy applied). Subjects will be categorized as "discontinued" if ablation was not possible due to non-investigational equipment failure, anatomy reasons or if their arrhythmia was determined at the time of electrophysiological study to be a non-study arrhythmia (e.g., atrial flutter).

- **Lost to Follow-up Subjects**: all subjects should be encouraged to return for protocol required office, clinic visit for evaluation during the study follow-up period. If a subject is unable to return for an office or clinic visit or unable to be contacted by telephone, 3 separate telephone calls should be made to obtain subject related safety information. All attempts should be documented in the source documents. If the subject does not respond to the 3 telephone calls, then the investigator must send a certified letter to the subject. If the subject does not respond to the letter, then the subject will be considered "lost to follow-up" for the current study visit. Subject contact must be attempted at each follow- up time point and if unable to contact the subject after 3 phone calls, the subject should once again be sent a certified letter. Only after failing to contact the subject at the final follow-up visit, the subject will be considered lost to follow-up and the study termination will be recorded in the individual case report form.

- **Withdrawn / Early Termination Subjects**: The investigator may remove a subject from the study for any of the following reasons: no longer meets eligibility criteria; withdrawal is in the subject's best interest; subject preference; concurrent illness; noncompliance; or any other situation the investigator deems a compromise to the integrity of the study. Subjects will be informed prior to study entry that they are free to withdraw from the study at any time and for any reason, without prejudice to his or her future medical care by the physician or the institution.

If a subject is removed from the study, the date and reason for withdrawal will be recorded on the appropriate case report form (CRF). If the subject is withdrawn due to an adverse event (AE) or serious adverse event (SAE), the Investigator must comply with all reporting requirements and must follow the subject until the AE/SAE has resolved or stabilized.

- **Completed Subjects**: enrolled subjects who have not expired or been discontinued, withdrawn or lost-to-follow-up from the study, prior to the final 1-year study visit.

3.7 Study Process

Sites participating in this study will be selected based upon their capabilities to successfully carry out those assessments. All patients considered for a RF ablation procedure for drug refractory recurrent symptomatic PAF should be screened by the investigator or designated member of the research team for study eligibility.

Pre-procedure assessments should be performed prior to the index AF ablation procedure. The AF ablation procedures for this study should follow 2012 CSPE fibrillation atrial treatment guidelines[2].

- Diagnostic catheter placement
- Electrophysiology study (under discretion of investigator)
- Transseptal puncture
- Cardioversion if subject is in AF (under discretion of investigator)
- Introduction of the Study Catheter
- CARTO® 3 mapping of the targeted Left Atrium (LA)
- Ablation of targets
- An isoproterenol intravenous challenge is required 0.5h after the CPVI procedure to confirm the entrance block and exit block

In the event of spontaneous or induced AF and/or atrial flutter, the placement of additional RF lesions outside of the PV ostia is at the discretion of the investigator. Any sheath except Agilis can be used in conjunction with ST catheter during the procedure. Cardioversion will be allowed if deemed clinically necessary by the investigator.

All subjects will be followed through one year after the index ablation procedure. Blanking period will span 90 days. After the index AF ablation procedure, subject follow-up visits are required at 3 months (Day 90: 76-104 days), 6 months (Day 180; 166-210 days), 9 months (Day 270; 240-300 days), and 12 months (Day 360; 330-420 days). Follow-up visit schedule will not reset if subject undergoes a repeat AF ablation procedure with the study catheter. At each visit, the following assessments should be performed: AF/AT/AFL recurrence and repeat ablation; ECG/24-hour Holter /TTM; Current AAD (including anticoagulation regime); Adverse events. The detail of the flow chart is shown in table 1.

Table 1: Data Collection flow chart

	Baseline/Pre-Ablation	**Ablation**	**Discharge**	**3M [Days 76-104]**	**6M [Days 166-210]**	**9M [Days 240-300]**	**12M [Days 330-420]**	**Unexpected follow-up[3]**
Visit	X			X	X	X	X	X
Informed Consent	X							
Demographics	X							
Medical history	X							
Ablation parameter values		X						
AF status	X		X	X	X	X	X	X
Previous and current cardiac medication	X		X	X	X	X	X	X
Current anticoagulation regime	X		X	X	X	X	X	X
ECG	X		X	X	X	X	X	X
24 h Holter	X			X	X	X	X	X
Examination to detect LA thrombi [1]	X							
TTM [2]				X	X	X	X	X
AF/AT/AFL recurrence				X	X	X	X	X
Repeat ablation				X	X	X	X	X
Adverse events		X	X	X	X	X	X	X

1. To detect LA thrombi, e.g. toutine TEE on the day or the day before AF ablation.
2. TTM transmission will be weekly during the first 8 weeks after the blanking period; After the first 8 weeks, asymptomatic transmissions will be transmitted monthly until the end of the 12-month follow-up visit. All symptomatic arrhythmia episodes should be recorded and transmitted at the time the event occurs.
3. If a subject returns for an arrhythmia related visit outside of the protocol-defined visit schedule provided, the visit will be considered "unscheduled" (UNS).

4 Study Endpoint

4.1 Primary Efficacy Endpoint

The primary effectiveness endpoint for this study is freedom from documented symptomatic

atrial fibrillation (AF), atrial tachycardia (AT), or atrial flutter (AFL) episodes through 12-month follow-up after the index ablation procedure (includes a three-month blanking period).

AF/AFL/AT qualifies as an arrhythmia recurrence after the first ablation if it lasts ≥30 seconds and is documented by ECG, HM or TTM, etc.

The following indicators will also be considered primary effectiveness failures and will be included in the effectiveness analysis population:

- Acute procedural failure (i.e., failure to confirm entrance block in all pulmonary veins with an isoproterenol intravenous challenge 0.5h post procedure or use of a non-study catheter to treat PAF)
- A repeat ablation beyond the 90-day blanking period

Atrial tachycardia/fibrillation atrial/auricular flutter recurrence events will be recorded and included in study analysis after a 90-day blanking period; recurrence during the blanking will not be considered treatment failure; re-ablation will not be recommended during the blanking [1,2].

4.2 Secondary Efficacy Endpoints

4.2.1 Acute Success Rate

Acute success is defined as confirmation of entrance block in all PVs with an isoproterenol intravenous challenge 0.5h post procedure.

The following test subjects will be considered as acute failures:

- Entrance block not confirmed for all PVs
- Subjects in whom a non-study catheter has been used for initial ablation of any AF targets

Acute failures will be considered primary effectiveness failures. Malfunction of a non-investigational catheter during the AF procedure will not be considered an acute failure.

4.2.2 CF and Force Time Integral (FTI) for index procedure by PV segments (from PV to the atrium, divided into 3, 6, 9 and 12 point position) (as shown in figure 1 below)

4.2.3 Number, percentage and sites of PV reconnection for the index procedure (from PV to the atrium, divided into 3, 6, 9 and 12 point position) (as shown in the figure below)

4.2.4 Total procedural time, ablation (RF) time and fluoroscopy time

4.3 Safety Endpoint

The incidence of AEs related with the procedure or study catheter

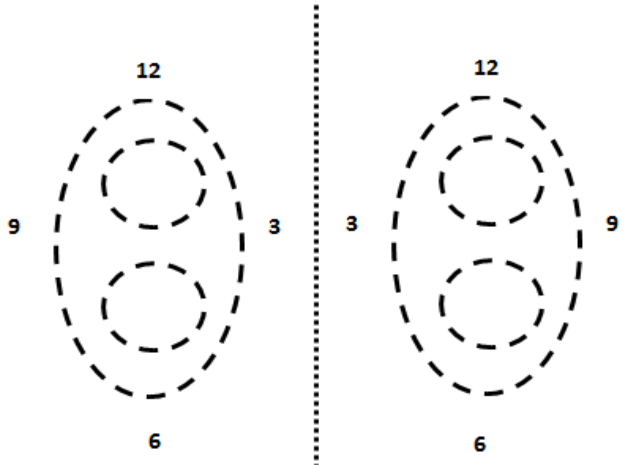

Figure 1: Right/left pulmonary veins was divided into 3, 6, 9 and 12 point position from PV to the atrium

5 Sample Size and Statistical Power

Assuming the true rate for freedom from documented symptomatic AF, AT, or AFL episodes through 12-months follow-up is about 65% using THERMOCOOL® SMARTTOUCHTM catheter with Contact Force Sensing Capability and a historic control performance goal of 50%, a sample size of 150 is needed in order to have 95% power to have the lower bound of the two-sided 95% confidence interval of this free-from-recurrence rate above the historic control performance goal[1]. The calculation formula[54] was refer to the paper written by Xinran Tang.

nQuery Advisor® version 7.0 is used for calculation of this sample size. Assuming the dropout rate of the study is 20%, 150/ (1-0.2) =188 subjects is needed in total. About 200 subjects are planned to be enrolled in this study (at least 188 subjects).

6 Data Analysis

6.1 General Principle

All statistical procedures will be completed using SAS version 9.2 or later version. Statistical methods applied will be mostly descriptive statistics.

The continuous variables will be summarized by the statistics listed in table 2:

Table 2: Descriptive statistics of quantitative measures

Statistics	Decimal place preserved
N (Total number of patients in treatment group)	0

n (Number of patients without missing values)	0
Mean, median, Q1, Q3	Preserve one more decimal place than the original data, up to no more than four decimal places
Standard deviation	Preserve two more decimal place than the original data, up to no more than four decimal places
Maximum, minimum	Preserve the same decimal place as the original data, up to no more than four decimal places

The categorical variables will be summarized with the frequency and percentage of each type. The missing value will not be included in the calculation of percentage, unless otherwise specified.

Kaplan-Meier method will be used for the time to onset of the first symptomatic AF, AT, or AFL episode. The statistics listed in Table 3 will be used to describe the results of statistical analysis model.

Table 3: Statistics of statistical analysis model

Statistics	Decimal place preserved
Q1, Q3, median	Preserve one more decimal place than the original data, up to no more than four decimal places
95% confidence interval	Preserve two more decimal place than the original data, up to no more than four decimal places
P-value	Usually preserve 3 decimal places (or <0.001, or >0.999)

Hypothesis testing will be carried out at the two-sided α=0.05 level unless otherwise specified, and 2-sided 95% confidence intervals will be presented.

6.2 Analysis Population

6.2.1 Intent-to-treat (ITT) Population

Intent-to-treat (ITT) Population: All enrolled subjects who meet the inclusion/exclusion criteria and have signed informed consent form.

ITT Population will be used for baseline summary and provide analysis for primary efficacy endpoints.

6.2.2 Safety Analysis (SS) Population

Safety Analysis (SS) Population: All enrolled subjects who have undergone insertion of the study catheter during the procedure.

Safety Population will be used for the summaries for safety endpoints, secondary efficacy endpoints and other procedural data.

6.2.3 Per-protocol (PP) Population

Per-protocol (PP) Population: Subjects in the ITT Population who have undergone insertion of the study catheter and AF ablation procedure, and do not have other major protocol violations. The definition of major protocol violations includes but not limited to:

- Serious violation of the inclusion/exclusion criteria, and the subjects are allowed to continue the clinical trial;
- Violation of informed consent (e.g.: no informed consent is conducted, the signature and/or the date of the informed consent form is missing; The time signed is after the procedure; Both the two copies of ICF are kept in the study site)
- No transesophageal echocardiography (TEE) examination is conducted within 24 hours before the procedure; (Applicable to the document "A Description of SMART CHINA Study Protocol Violations/Deviation Report to Institutional Ethics Committee(IEC)" developed on June 20, 2015)
- No examination to detect LA thrombi is conducted before the procedure; (Applicable to the document "A Description of SMART CHINA Study Protocol Violations/Deviation Report to Institutional Ethics Committee(IEC)" developed on January 18, 2016)
- THERMOCOOL® SMARTTOUCH™ catheter is not used or is used repeatedly during the procedure
- CARTO®3 V3.2 or the later version and VisiTag™ software is used for data collection during the procedure
- No isoproterenol is used to confirm entrance block 30 minutes after the procedure
- Agilis sheathing canal in combination with THERMOCOOL® SMARTTOUCH™ catheter is used during the procedure

Repeated ablation treatment is conducted during the blanking period, PP population will be used to provide supportive analysis for efficacy endpoints.

6.3 Study Objects

6.3.1 Study Completion Condition

The screening subjects and enrolled subjects, as well as the subjects who complete the study will be summarized The reasons for screening failure and early termination will be classified and summarized.

All the subjects with failed pre-procedure screening will be listed, and the subjects' ID, age,

gender, date of screening failure and the reason for screening failure are explained by study site. All of the subjects with early termination will be listed, and the subjects' ID, age, gender, beginning date, ending date and the duration in the study and the reason for early termination are explained by study site.

6.3.2 Protocol Deviation

Major protocol deviation will be summarized, and the follow-up period and reason for major protocol deviation will be classified and summarized. List of major protocol deviation will also be presented.

6.3.3 Demographic and Baseline Characteristics

The patients' demographic characteristics (age, gender and nationality) are summarized and described. The qualitative indicators are summarized with frequency and percentage, and the quantitative indicators are summarized with descriptive statistics (mean, standard deviation, median, maximum and minimum, Q1 and Q3). The demographic and baseline characteristics need present for all enrolled subjects and ITT population.

The baseline characteristics shown below are analyzed with the descriptive method similar to that used for demographic characteristics:

1) History of fibrillation atrial, including:

- Symptomatic fibrillation atrial history (month) according to the initial PAF symptom or record
- Average duration (hour) per episode within 12 months before enrollment
- Average frequencyof episodes (times/month)
- Objective evidence of confirmed fibrillation atrial within 12 months before enrollment: surface electrocardiogram (ECG), 24-hour dynamic electrocardiogram (24 Holter), transtelephonic monitor (TTM) and others
- Presence of fibrillation atrial related symptom
- Fibrillation atrial/ Atrioventricular tachycardia/ auricular flutter (AF/AT/AFL status)
- Paroxysmal or persistent fibrillation atrial related symptom

2) Medical history – underlying heart disease, including:

- Presence of definite organic heart disease
- Type of organic heart disease

- Cardiac function NYHA grading
- Presence of other complications
- Type of other complications
- Presence of thrombotic disease history
- Type of thrombotic disease history
- Presence of hemorrhagic disease
- Presence of diabetes
- Presence of other arrhythmia symptoms
- Type of other arrhythmia disease

3) Echocardiography

- Whether the subject has undergone transesophageal echocardiography (TEE) examination within 24 hours before the procedure
- Presence of atrial thrombosis
- Whether the left atrial diameter has been tested?
- Left atrial diameter (LAD) (cm)
- Whether the subject has undergone trans thoracic echocardiography (TTE) examination?
- Whether the ultrasound cardiography shows left ventricular ejection fraction
- Left ventricular ejection fraction (LVEF) (%) showed with echocardiography

4) Treatment of fibrillation atrial and other heart diseases, including:

- Whether the subject has taken antiarrhythmic drugs within the past 3 months
- Whether the drug has been stopped for 5 half-lives
- Whether the subject has taken anticoagulant drugs within the past 3 months
- Whether the subject has taken other cardiac drugs within the past 3 months
- Whether the subject has received electrical conversion treatment before the procedure due to fibrillation atrial
- The times of electrical conversion

5) ECG examination, including:

- Heart rhythm
- With or without atrioventricular block
- The grade of atrioventricular block
- Bundle branch block
- The type of bundle branch block

6) 24-hour dynamic electrocardiogram (24 Holter) examination, including:

- Heart rhythm

7) Transtelephonic monitor (TTM), including

- Heart rhythm
- Whether the fibrillation atrial symptom occurs during monitoring

Among the abovementioned characteristics, fibrillation atrial/ atrioventricular tachycardia/auricular flutter, ECG examination, 24-hour dynamic electrocardiogram (24 Holter) examination, and transtelephonic monitoring (TTM) will be described and analyzed together with each follow-up time point. At each follow-up time point, if the AF/AFL/AT arrhythmia recurrence lasts ≥30 seconds and is documented by ECG, 24-Holter or TTM, the examination characteristic will be summarized as well.

All the baseline data collected in the CRF will be tabulated and explained.

6.3.4 Concomitant Medication

The cardiac drugs and other drugs used during treatment is described and analyzed. The cardiac drugs will be further classified and described by antiarrhythmic drugs, anticoagulants and other cardiac drugs. The cardiac drugs and other drugs will be coded with World Health Organization drug dictionary (WHODRUG) and Anatomical Therapeutic Chemical classification (ATC), and will be classified, summarized and described with ATC Level IV and Preferred Name, respectively.

Meanwhile, the previous drugs and concomitant drugs will also be described and analyzed, respectively. The previous drugs are defined as the drugs that have been stopped before the beginning of the study. The concomitant drugs are defined as the drugs that are used after the beginning of the study, or those have been used before the study, but are continued after the beginning of the study.

6.4 Ablation Parameters

Descriptive analysis is conducted for ablation procedure parameters, and the procedure parameters include:

- Total X-ray fluoroscopy dose (mGr)
- Intraoperative transcatheter fluid infusion (ml)
- The maximum infusion rate of the intraoperative transcatheter fluid (ml/min)
- Whether the subject has been observed for 30 minutes after CPVI
- Whether isoproterenol has been given to induce fibrillation atrial 30 minutes after CPVI
- Whether other drugs have been given to induce fibrillation atrial 30 minutes after CPVI
- Whether an immediate success has been achieved
- Whether the exit block has been observed
- Presence of linear ablation
- Presence of other ablation
- Whether the sheathing canal has been used during the procedure
- Whether CART03 version 3.2 or later version has been used to mapping the left atrium before radiofrequency ablation
- Whether the VisiTag module has been used
- Whether radiofrequency discharge is conducted
- Average power (watt)
- Average temperature (C)
- CF
- Number of PV reconnection targets
- Procedual time, ablation time and fluoroscopy time
- The longest duration of one-time single discharge (second)
- The maximum decrease in impedance value (ohm)
- Presence of any other types of spontaneous arrhythmia during the procedure

- Presence of any other types of induced arrhythmia during the procedure

6.5 Effectiveness Analysis

6.5.1 Primary Efficacy Endpoint Analysis

ITT population is used for the main analysis of the primary endpoint, and PP population is used for supportive analysis.

The primary endpoint for this study is freedom from documented symptomatic AF, AT, or AFL episodes through 12-months follow-up after the index ablation procedure (includes a 3 months blanking period).

The following will also be considered primary effectiveness failures and will be included in the effectiveness analysis population:

- Acute procedural failure (i.e., failure to confirm entrance block in all pulmonary veins with an isoproterenol intravenous challenge 0.5 h post procedure or use of a non-study catheter to treat the study arrhythmia);
- A repeated ablation after the 90-day blanking period

Atrial tachyarrhymia recurrence events will be recorded and included in study analysis after a 90-day blanking period. Recurrence during the blanking will not be considerd treatment failure.

The number of subjects who achieved this endpoint and its percentage will be presented. A two-sided binomial exact 95% confidence interval will be computed. Superiority against historic control performance goal (50%) after applying THERMOCOOL® SMARTTOUCH™ catheter with contact sensitivity will be claimed if the lower bound of this confidence interval is above 50%.

For the subjects failing to be followed up to the primary endpoint, with conservative consideration, these subjects are considered as primary effectiveness endpoint failure in the main analysis.

Sensitivity analysis will be conducted for the primary endpoints using the methods below:

- For the subjects failed to be followed up to the primary endpoint, the primary endpoint is considered as missing in the analysis, and the subjects will be excluded from ITT analysis set.

A Kaplan-Meier analysis will be performed for the time to the first documented symptomatic AF, AT, or AFL episode. The first quartile, median, third quartile and 95% confidence intervals of the first quartile, median and the third quartile will be computed.

Kaplan-Meier curves for episode time of symptomatic AF, AT or AFL first recorded during 12 months follow-up (Day 91 to 361) after the first ablation will be presented.

Logistic regression method will be used to analyze the effect of baseline variables and procedure parameters on the primary effectiveness endpoint. For the influence factor of episode rate, univariate logistic regression analysis model will be first used for preliminary screening of influence factors, of which, the influence factor with p-value <0.2 will be placed into multiple factor regression model for further analysis; and step-wise regression method will be used for further variable screening, of which, the influence factor with p-value <0.2 will be removed from multiple factor model. Please refer to baseline characteristics in Section 6.3.3.

Repeat ablation beyond the blanking period will be described and summarized.

6.5.2 Secondary Efficacy Endpoint Analysis

For acute success rate, the number of subjects who achieved this endpoint and its percentage will be presented. A two-sided binomial exact 95% confidence interval will be computed.

For CF and Force Time Integral for index procedure by PV segments, descriptive summary statistics and 95% confidence intervals will be presented. For CF, the frequency distribution will be summarized and plotted by an increment of every 5 gramas a group. The frequency distribution of selected CF range in different sites will be summarized and plotted. Only need to present to 1 decimal place for mean, median, Q1, Q3, min and max for CF.

For PV reconnection after the index procedure, descriptive summary statistics will be presented. Frequency counts and percentages will be used to summarize the sites of PV reconnection. A two-sided binomial exact 95% confidence interval will be computed. Proportion of PV reconnection after the index procedure will be computed for each subject. And then the descriptive summary statistics and 95% two-sided asymptotic confidence intervals will be used to summarize the proportion of PV reconnection across subjects. Formula for proportion of PV reconnection for each subject is:

(Number of PV **reconnection targets / Total number of ablation targets)* 100**

For total procedural time, ablation time and fluoroscopy time, descriptive summary statistics and 95% confidence intervals will be presented.

6.5.3 Other Analysis

Correlation between the CF and the primary efficacy endpoint will be presented.

- Average CF
- CF ranges

- CF groups (<14 g and >= 14 g)

Rank-sum test will be used to calculate the p-value of continuous variables, and Fisher's Exact Test will be used to calculate the p-value of categorical variables.

6.5.4 Cardiac Related Examination Results

Fibrillation atrial/atrioventricular tachycardia/auricular flutter, ECG examination, 24-hour dynamic electrocardiogram (24 Holter) examination, and transtelephonic monitoring (TTM) at each follow-up time point will be described and analyzed (the specific content is the same as the baseline), and tabulated and explained. The main symptoms and information of examination for discharge and follow-up will be tabulated and analyzed.

Per the study protocol, subjects were required to transmit a minimum of 15 TTM recordings during the 9-month evaluation period. Subjects were required to record and transmit at least one cardiac episode per week for the first 8 weeks of the 9-month evaluation period. After the first 8 weeks, subjects were required to transmit cardiac episodes at least once a month until the effectiveness assessment period was completed. In addition, subjects were asked to record and transmit all symptomatic cardiac episodes.

According to the prorocol and CRF, 4 follow-ups timepoints which recorded in the CRF will be presented, including 3rd month, 6th month, 9th month and 12th month follow-up. So there may be several TTM examinations during a follw-up timepoint. Each of the TTM result need to be considered.

6.6 Safety analysis

Adverse events will be encoded to System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities MedDRA, version 18.0.

The analysis of adverse events will be based on treatment emergent adverse events (TEAE). An AE will be considered TEAE if (1) the AE has started on or after the date of the ablation procedure, or (2) the AE has started before the procedure but has worsened in severity on or after the date of the procedure.

All TEAEs, and TEAEs related with study device or ablation procedure, serious adverse events (SAEs), and SAEs related with study device or ablation procedure will be summarized and analyzed.

The number of subjects with TEAEs and the number of the events will be classified and described with System organ classification (SOC) and preferred term (PT), respectively.

Similar summary will be provided for the TEAEs related with study device or ablation procedure,

SAEs and SAEs related with study device or ablation procedure. At the same time, similar summary will be provided for TEAEs that occurred within 7 days of a study ablation procedure.

All the TEAEs, the serious adverse events leading to death, and all the serious adverse events are tabulated and analyzed in detail.

The number and percentage of subjects with TEAEs and SAEs will be summarized overall and by AE type, timing, seriousness, severity, causality, anticipated or not and outcome. Listing of AEs will also be provided.

7 Interim analysis

An interim analysis will be conducted in this study. The time of interim analysis is designated to be March 31, 2016, and the main aim is to provide summary descriptive statistics for baseline and procedure data. The results of interim analysis will not be used to change the sample size or discontinue the study.

The main content included in this interim analysis will be provided separately in another document.

8 Changes to planned analytical methods of the protocol

None.

9 Data processing principle

None.

10 PROGRAMMING SPECIFICATIONS

Programming specifications will be provided separately in another document.

11 MOCK TABLES, LISTINGS AND GRAPHS of statistical analysis

Mock tables, listings and graphs of statistical analysis will be provided separately in another document.

12 References

1-53, Please refer the references in the protocol

54. Xinran Tang. 样本量估计及其在 nQuery 和 SAS 软件上的实现-率的比较（一）. Chinese Journal of Health Statistic. 2012.10, 29(5): 754-758.

13 Appendix

None.