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STATISTICAL ANALYSIS PLAN

Protocol Title:	Atrial Fibrillation Progression Trial (ATTEST Trial)
Protocol Number:	144 Version 3.0 (9-Apr-2013)
Device:	CARTO® 3, CARTO® XP or CARTO® RMT System and THERMOCOOL® Catheter Family
Phase:	Post-marketing Study
Sponsor:	BIOSENSE WEBSTER, INC. 3333 Diamond Canyon Road Diamond Bar, CA 91765 USA
SAP Author:	[redacted]
SAP Version:	FINAL Version 2.0
SAP Date:	08-NOV-2018

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STATISTICAL ANALYSIS PLAN DOCUMENT HISTORY

Version	Date	Author	Description
Final 1.0	12-JAN-2016	[redacted]	Original
Final 2.0	08-NOV-2018	[redacted]	SAP update after study was terminated early • Clarifications concerning primary endpoint analysis added • Sensitivity analysis for alternative definition of primary endpoint and first secondary endpoint added • Some of the analyses originally planned in the protocol removed • Minor updates based on shell development

SIGNATURE PAGE AND APPROVALS

[redacted]

[redacted]

Date

[redacted]

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ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
AAD	Antiarrhythmic Drug
ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect on Quality-of-life (AFEQT) Questionnaire
ARDS	Acute Respiratory Distress Syndrome
AT	Atrial Tachycardia
ATC	Anatomical Therapeutic Chemical
BB	Beta Blocker
CABG	Coronary Artery Bypass Graft
CCB	Calcium Channel Blocker
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CP	Conditional Power
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
CV	Coefficient of Variation
CVA	Cerebrovascular Accident or Stroke
GSMC	Global Safety Monitoring Committee
EB	Ethics Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMEA	Europe, Middle East and Africa
EP	Electrophysiology
EQ-5D	EuroQoL 5 Dimensions
FDA	Food and Drug Administration
Fr	French

ABBREVIATION	DEFINITION OR DESCRIPTION
GCP	Good Clinical Practices
GEE	Generalized Estimating Equations
HM	Holter Monitoring
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instruction For Use
ILR	Implantable Loop Recorder
ISO	International Organization for Standardization
ITT	Intent to Treat
KM	Kaplan-Meier
LA	Left Atrium
LV	Left Ventricle
MDR	Medical Device Reporting
MDV	Medical Device Vigilance
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NYHA	New York Heart Association
PAF	Paroxysmal Atrial Fibrillation
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
PP	Per Protocol
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QoL	Quality Of Life
RA	Right Atrium
RF	Radiofrequency
RSPV	Right Superior Pulmonary Vein
RV	Right Ventricle
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
SR	Sinus Rhythm
TEE	Transesophageal Echocardiography

ABBREVIATION	DEFINITION OR DESCRIPTION
TIA	Transient Ischemic Attack
TLG	Table, Listing, Graph
TTE	Transthoracic Echocardiography
TTM	Transtelephonic Monitoring
UADE	Unanticipated Adverse Device Effect
WHO	World Health Organization
VAS	Visual Analogue Scale

1. SYNOPSIS

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Biosense Webster ATTEST protocol "Atrial Fibrillation Progression Trial" dated 9-Apr-2013 Version 3.0.

This post-marketing trial is a prospective, multi-center, randomized, controlled, two-arm, open-label, clinical study to determine whether early radiofrequency (RF) ablation treatment, using the CARTO® 3, CARTO® XP or CARTO® RMT System, and THERMOCOOL ® Catheter Family in subjects with Paroxysmal atrial fibrillation (PAF), delays progression of atrial fibrillation (AF) compared with drug therapy (either rate or rhythm control) using current AF management guidelines.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

The following documents were reviewed in preparation of this SAP:

- Clinical Research Protocol Number 144, Version 3.0 dated 9-Apr-2013
- Case report forms (CRFs), Version 2.1 dated 01-Jul-2013

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objective

The objective of this study is to determine whether in subjects with Paroxysmal AF (PAF), early RF ablation treatment using the THERMOCOOL® Catheter Family in conjunction with the CARTO® 3, CARTO® XP or CARTO® RMT System delays progression of AF compared with drug therapy (either rate or rhythm control) using current AF management guidelines.

2.2 Efficacy, Safety and Health Economic Endpoints

2.2.1 Efficacy Endpoints

The primary efficacy endpoint is the time to persistent AF/AT (excluding isthmus-dependent atrial flutter) at 3 years. According to the protocol, persistent AF/AT is defined as AF/AT lasting longer than 7 consecutive days or requiring termination by cardioversion after 48 hours.

Secondary efficacy endpoints are:

- Rate and time to persistent AF/AT at 1 year and 2 years, rate of persistent AF/AT by number of ablations at 3 years
- Number of repeat ablations and new anti-arrhythmic drugs (AAD) per subject throughout 3 years follow-up

- Rhythm (% subjects in sinus rhythm (SR), % subjects with recurrent AF/AT) throughout 3 years follow-up
- Factors associated with AF disease progression
    - Gender
    - Age
    - Left atrium (LA) size
    - HATCH score (score based on the five components: Hypertension, Age 75 years or older, Previous transient ischemic attack or stroke, Chronic obstructive pulmonary disease, and Heart failure)
    - Blood pressure
    - NYHA functional classification of heart disease
    - Presence of diabetes
    - Presence of hyperlipidemia or dyslipidemia
    - Presence of renal insufficiency
    - Presence of dementia

In addition, an alternative definition of the primary and the first secondary endpoint will be investigated based on the consensus statement of the HRS (Heart Rhythm Society, 2017). According to the HRS consensus statement 2017, persistent AF/AT is defined as continuous AF/AT that is sustained beyond 7 days.

2.2.2 Safety Endpoints

The key safety endpoints are:

- Catheter-related complications (adverse events)
- Drug related Adverse events-Adverse Drug Reactions (ADR)

2.2.3 Health Economic and Quality of Life Endpoints

The health economic endpoints are:

- Health care utilization (number and length of hospitalizations and unscheduled cardiovascular-related visits)
- Quality of Life (QoL) at 3 months, 6 months, 1 year, 2 years, and 3 years by change from baseline in
    - EQ-5D Score
    - AFEQT Score (collected in a subset of countries)

3. STUDY METHODS

3.1 Overall Study Design and Plan

ATTEST is a post-marketing, prospective, multi-center, randomized, controlled, two-arm, open-label, clinical study. For subjects randomized to the ablation group (Test), physicians are to perform procedures per institutional Standards of Care and processes required by their institution. For subjects randomized to the AAD group (Control), physicians are to manage medication in accordance with published, current

AF Management and with the Standard of Care and procedures required by their institution.

All subjects will be followed through 3 years. A subject in the medication group may request a cross-over to receive ablation

3.2 Selection of Study Population

This is a post-marketing study in subjects with Paroxysmal AF (PAF). Key inclusion criteria identified in the protocol are:

- Subjects with recurrent paroxysmal AF for at least 2 years, with ≥ 2 episodes over the last 6 months
- HATCH Score of at least ≥1 and ≤ 4
- Eligible for catheter ablation and for anti-arrhythmic or rate control medications, after having failed at least one but no more than 2 prescribed drugs (either anti-arrhythmic or rate control drug)
- Age 60 years or older
- LA diameter ≤ 55 mm by Transthoracic Echocardiography (TTE)
- Left ventricle (LV) ejection fraction ≥ 50% when in sinus rhythm or LV ejection fraction ≥ 35% when in AF
- Subject signed the Informed Consent Form and is able and willing to comply with protocol requirements, including all baseline and follow- up testing.

For the complete list of in- and exclusion criteria see the CTP, Sect. 9.3 and 9.4.

3.3 Method of Treatment Assignment and Randomization

Subject randomization will be 1:1 between catheter ablation (Test) and AAD therapy (Control). The randomized block design, stratified by gender and site, will be used to ensure a gender balance by treatment group at each site. Adaptive randomization will also be executed to further ensure the allocation balance of treatment groups by gender at each site. Subjects will be randomized in the order of their enrollment.

3.4 Treatment Masking (Blinding)

This is an open-label study.

4. ANALYSES AND REPORTING

4.1 Interim Analyses

An interim examination of the primary endpoint data will be performed at regular time intervals during the course of the trial to determine whether the study will be stopped for effectiveness or futility. Interim analyses will only be presented for the ITT and Safety Population. At the first interim analysis, sample size adjustment will be considered as specified in section 5. In addition, statistical interim reporting will also involve a review of adverse events. The results of the interim analyses will be reviewed by the Global Safety Monitoring Committee (GSMC) of Biosense Webster.

The GSMC will review the accumulated data no earlier than 1 year following the

study start and then approximately every 6 months thereafter if enrollment was on target. Data for the primary effectiveness endpoint and adverse events will be reviewed. Extracted data files and analysis programs for each interim report will be archived in the study files. Further details on the planned interim analyses are given in section 10.4. Moreover, it is indicated in the table of contents (section 15) which subset of tables, listings and figures will also be produced for the interim analysis.

4.2 Final Analyses

All final planned analyses identified in the protocol and in this SAP will be performed only after all relevant study data have been processed and the database has been locked. In addition, no database may be locked, random code unblinded, or analyses completed until this SAP has been approved.

Key statistics and study results will be made available to Biosense Webster following database lock and prior to completion of the final CSR.

Any post-hoc exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses (post-hoc) will also be clearly identified in the text of the CSR.

4.3 SOPs

The following Premier statistics SOPs are applicable for this study:

SOP Number	SOP Title
SOP-ST-45.01	Statistical Analysis Plan
SOP-ST-47.01	Planning Execution and Delivery of Statistical Analyses
SOP-ST-48.01	Unblinding a Study for Statistical Analysis
SOP-ST-46.01	Development and Validation of SAS Programs

5. CHANGES TO PLANNED ANALYSIS

5.1 Changes for the final analysis

As the study was terminated early, without having met primary effectiveness or futility criteria at the most recent interim analysis, it is not fully obvious which alpha level to use for the primary efficacy analysis. However as the number and time points of the interim analyses had not been fixed in advance, it was decided to spend all alpha remaining for the final analysis, in other words to spend what is left from the total alpha. Moreover, after further discussion, it has been decided to update the calculation of the primary endpoint to use procedure date as start date for time to event calculation rather than randomization date (see section 8.3).

It also was decided to delete some of the analyses originally planned in the protocol:

- For secondary endpoint "factors associated with AF disease progression", only the main analyses will be performed, and some of the supporting models were deleted
- Analysis of site heterogeneity will not be performed

Moreover, a sensitivity analysis for the primary endpoint and first secondary endpoint was added, using an alternative definition for the primary endpoint based on the consensus statement of the HRS (Heart Rhythm Society, 2017).

5.2 Changes for the interim analyses

Before the first interim analysis, some updates had been made to the orginally planned method for re-calculation of operating characteristics. Section 10.4 reflects those updates.

6. SAMPLE SIZE DETERMINATION

A total sample size of 322 (161:161) subjects will be required to ensure 85% power to detect the effect size measured by negative log of the hazard ratio equal to 1.1541 (treatment group over control group).

$$-\log_e\left(\frac{\hat{\lambda}_t}{\hat{\lambda}_c}\right) = -\log_e\left(\left(-\frac{\log_e(0.95)}{3}\right)/\left(-\frac{\log_e(0.85)}{3}\right)\right) = 1.1541$$

This calculation assumes a 50% cross-over rate from the AAD group to the ablation group, a 10% drop-out rate in each group over the 3 year follow-up period, and 1.5 years accrual time. This calculation is based upon one-sided superiority testing with alpha equal to 0.025. Using meta-analysis, the rates of disease progression at the end of follow-up are estimated to be 25% and 5% in the AAD and ablation group, respectively (see the point estimate justification document for details, Appendix C of the CTP). The cross-over to ablation is reflected in the use of the proportion 0.85 instead of 0.75 in the formula above. The sample size calculation is based upon the method developed by Rubinstein, Gail and Santner[4] (RGS, 1981) and also incorporates group sequential design with multiple interim looks.

Adaptive Sample Size Re-estimation

Due to the uncertainties associated with the cross-over rate and the effect size, the sample size will be reestimated at the time of the first interim analysis. Conditional power (CP) will be calculated at that time to determine how promising the interim results are. CP is defined as the conditional probability that the final result will exceed a critical value given the data observed thus far, and the assumption that the trend to be observed in the remainder of the study[5]will follow the expectation, which was used in the original sample size calculation. If the CP is less than 0.3, then the study is considered not promising, and the sample size will not be increased. If the CP is

greater than 0.9, then the study is deemed fully powered and the sample size will not be increased. If the CP falls in the promising zone (0.3-0.9), the sample size will be re-estimated based upon the observed effect size.

In detail, the following formula will be applied to re-estimate the sample size:

$$M = N\left(\frac{\delta}{\Delta}\right)^2$$

where M is the updated sample size per group, N is the initially planned sample size per group, δ is the expected effect size (1.1541) and Δ is the effect size observed at the time of interim analysis:

$$\Delta = -log_e\left(\frac{D_t/T_t}{D_c/T_c}\right)$$

where D_t and D_c are the number of deaths observed in the treatment and control group and and T_t / T_c are the total times observed (up to the time of censoring) in the respective groups.

In case the re-estimated sample size is unrealistic high, the sponsor will select one of the following 3 options:

- Determine the maximum realistic sample size and continue the study to enroll the maximum number of patients
- Continue study as planned to enroll original planned sample size
- Stop the study for futility.

In case the sample size will be increased, the CHW (Cui, Hung and Wang) adaptive method will be used for statistical testing.[6]

The CHW weighting will be applied according to the following formula:

$$Z = \sqrt{t_{adj}}Z_{0;adj} + \sqrt{(1 - t_{adj})}Z_{adj;max}$$

Where Z is the final test statistic, t_{adj} is the (planned) information fraction at the time of sample size adjustment, $Z_{0;adj}$ is the test statistic derived from the data available at the time of sample size adjustment, and $Z_{adj;max}$ is the test statistic derived from data collected after the time of sample size adjustment, including a possibly increased sample.

7. ANALYSIS POPULATIONS

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

Cross-over subjects will be handled differently for each type of analysis population, as described subsequently. In general, subjects from the control group who have an ablation procedure after the primary endpoint is met will not be analyzed as cross-over.

Intent to treat (ITT) population: The ITT subject population will include all

subjects randomized, where subjects will be classified by the group to which they are randomized, regardless of the treatment received. For the ITT population, cross-over subjects will be included in the Control Group per randomization. Lost-to-follow-up and withdrawn/early termination subjects will also be included in the ITT population.

Per protocol (PP) population: The PP subject population will include randomized subjects who satisfy the following criteria, according to the treatment actually received:

- **Test Group:** subjects who
  - have undergone RF ablation,
  - are treated with the study catheter (THERMOCOOL ® Catheter Family),
  - are in compliance (no major protocol deviations that has an impact on scientific value of the study) with the study protocol, and
  - have been treated for the study-related arrhythmia.
- **Control Group:** subjects who
  - have started an investigator-prescribed AAD and completed the dose-loading period (2 weeks),
  - have not undergone RF ablation,
  - are in compliance (no major protocol deviations that have an impact on scientific value of the study) with the study protocol, and
  - have been treated for the study-related arrhythmia.

All analyses conducted in the PP population will be as treated analyses. For descriptive tables and simple inferential models with fixed treatment effectsubjects who have undergone RF ablation will be included in the Test Group regardless of the original treatment assigned (original randomization). Thus, cross-over subjects will be included in the Test Group for PP analyses. For more complicated inferential analyses, models will be applied where treatment itself is included as time-dependent covariate (see section 10.2 and 10.6.4). The approach described above applies for all tables which do not summarize data by visit (e.g. for time to event endpoints and other endpoints calculated overall per-patient). For summaries by visit and repeated measurement models, cross-over subjects will be completely excluded.

Safety Population: The Safety Population will include all subjects who have undergone insertion of an ablation catheter, either as Test Group or cross-over subjects; and, subjects who started an investigator-prescribed AAD in the Control Group and did not initiate ablation therapy. Analysis of catheter-related complications will be limited to include only subjects who initiated ablation treatment (catheter insertion) either as Test Group and cross-over subjects.

Adverse drug reactions will be analyzed overall for all the subjects who have taken investigator-prescribed AAD and analyzed separately for cross-over subjects, those in the Test and Control Groups (excluding cross-over subjects).

8. GENERAL ISSUES FOR STATISTICAL ANALYSIS

8.1 General Statistical Methodology

Descriptive summaries will be provided where appropriate for each of the primary and secondary variables. Tables in the ITT population will summarize data by randomized treatment, tables in the PP and Safety populations will summarize data by treatment actually received if not otherwise specified.

Primary and secondary effectiveness analysis will be conducted in the ITT and the PP populations. All safety data analyses will be performed in the Safety Population.

Health economic and QoL tables will be completed for the ITT population unless otherwise specified. According to the protocol it was planned to use the PP population for health economic and QoL tables, but this was changed to ITT population to perform the analysis based on the randomized treatment groups.

Continuous, quantitative, variable summaries will include the number of subjects (N) with non-missing values, mean, standard deviation (SD), median, minimum, maximum, and quartiles, unless otherwise specified.

Categorical, qualitative, variable summaries will include the frequency and percentage (where applicable) of subjects who are in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment groups unless otherwise specified.

The baseline value will be defined as value entered to the screening/baseline page of the eCRF (terminology screening/baseline is not used consistently in eCRF, but there is only one screening/baseline assessment planned according to protocol).

All analyses will be performed using SAS® Software version 9.1.3 or later. ADDPLAN® version 5.0.2 or later and East version 5.3 or later may also be used.

For re-calculating of operating characteristics for the analyses of the primary endpoint, the software WinLD will be used.

8.2 Handling of Missing Data

There will be no imputation for the primary efficacy analysis and no sensitivity analysis with multiple imputation for the ITT population as the log rank test accounts for censored (independent of the reason) observations, which is sufficient also for subjects who could not be followed up for the planned period. Other data except treatment group assignment are not required for this testing method.

For the per protocol sensitivity analysis, the same applies to the time-to-event outcome (effectiveness endpoint) data.
For the derivation of the variable ‘duration of AF’, incomplete dates will be imputed with the mid point of the possible interval (15th of a month if only the day is missing, 1st of July if the month is missing as well). No further imputation is planned.

8.3 Derived Variables

Duration of AF [months]
Time between the recorded date of first AF and the date of randomization.

Time to persistent AF/AT
According to protocol, persistent AF/AT is defined as AF/AT lasting longer than 7 consecutive days or requiring termination by cardioversion after 48 hours.The primary endpoint is reached at the date of the first cardioversion after randomization (except cardioversion solely as part of a (re-)ablation procedure) or detection of persistent AF/AT by transtelephonic monitoring (TTM, performed between month 3 and month 36). The sponsor will review and adjudicate all events (progressions to persistent AF/AT), which were reported by the Investigator. Adjudication will already be performed for the interim analyses. All events where the sponsor confirmed in their final assessment that the primary endpoint was reached will be taken into account for analysis. The date at which the primary endpoint was reached will be taken as adjudicated by the sponsor or as reported by the Investigator (if no sponsor adjudicated date is available).
The protocol is not specific about the start date for time to event calculation. Originally according to SAP version 1.0 (which was applied for the interim analyses) time to event had been defined as the difference between randomization date and the date at which the endpoint was reached. However, after further discussion, it was decided to update the start date for time to event calculation for final analyis and to use date of procedure as start date for the test group, and date of randomization as start date for the control group.

This approach seems to be more appropriate and more conservative, as visit windows are calculated from date of procedure for test group. Otherwise, if time to event was calculated from date of randomization, test group would have longer follow-up period and longer time to each follow-up visit as control group.

If the primary endpoint is not observed during follow-up time, subjects will be regarded as censored at the completion visit/ last visit or at the last time TTM was recorded, whichever is later.

Time to persistent AF (HRS 2017)

According to the HRS consensus statement 2017, persistent AF is defined as continuous AF that is sustained beyond 7 days. The sponsor will provide an additional adjudication using this alternative definition of time to persistent AF. Based on this additional adjudication, a sensitivity analysis for time to persistent AF based on HRS 2017 will be performed.

AFEQT
Several summary scores will be derived from the responses to questions 1 to 20 of section 2 of the AFEQT questionnaire, for each of which responses between 1 (most desirable outcome) and 7 (least desirable outcome) can be given.

Using the following statistics, the scores are defined below:

- S(a,b) is the sum of responses for the range of questions between a and b (both a and b included)
- N(a,b) is the number of responses given for the range of questions between a and b (both a and b included)

- AFEQT Overall Score = 100 – (((S(1,18) – N(1,18))*100) / (N(1,18)*6))
- AFEQT Symptoms Subscale Sore = 100 – (((S(1,4) – N(1,4))*100) / (N(1,4)*6))
- AFEQT Daily Activites Subscale Score =
  = 100 – (((S(5,12) – N(5,12))*100) / (N(5,12)*6))
- AFEQT Treatment Concern Subscale Score =
  = 100 – (((S(13,18) – N(13,18))*100) / (N(13,18)*6))
- AFEQT Treatment Satisfaction Subscale Score =
  = 100 – (((S(19,20) – N(19,20))*100) / (N(19,20)*6))

EQ-5D

The EQ-5D questionnaire collects the EQ-5D visual analogue scale (VAS) score on a scale between 0 and 100 and five single items (mobility, self-care, activity, pain, and anxiety) with three response levels each (no problems, some problems, extreme problems). A summary score (EQ-5D health index) based on these five items will not be calculated, as this would require rather complex modelling using country-specific weights.

9. STUDY SUBJECTS AND DEMOGRAPHICS

9.1 Disposition of Subjects and Withdrawals

All subjects who provide informed consent will be accounted for in this study.

Disposition and study population summaries will be presented for all enrolled subjects by randomized treatment groups. Enrolled subjects are defined according to study protocol section 9.5 as subjects who sign the study informed consent form and are randomized. Thus, the set of enrolled subjects corresponds to the ITT population.

Descriptive summaries of population data will include the following:

- The number of subjects in each study population (ITT, PP, and Safety) will be summarized overall, by treatment group, and by study site.
- A listing sorted by randomized treatment group and subject will be provided that will include the reasons for exclusion from any of the study populations and the treatment assignment for the PP and Safety Population analyses.
- The number of subjects enrolled, excluded, discontinued, prematurely withdrawing from the study, lost to follow-up, died, not completed due to AE,

not completed due to other reasons, completed and the reasons for classification will be summarized.

- A listing of disposition as described above, including further details if available, will be provided for subjects in the ITT population.

A listing of screening failures (which are not randomized) with reason for screening failure will also be added.

9.2 Protocol Violations and Deviations

Protocol deviations are captured in the CRF on a specific protocol deviation CRF page.

Incidences of all protocol deviations reported in the CRF will be summarized by protocol deviation code. A listing of these protocol deviations will also be included.

Each protocol deviation entered to the eCRF will be classified by the sponsor into major and minor from study conduct perspective. The sponsor assessment will be included in the data base extract.

A major deviation will not automatically lead to exclusion of a subject from PP population. Generally, it is planned to exclude a subject only from PP population in case of a major protocol deviation related to inclusion or exclusion criteria. To make a final decision, the sponsor will review all cases with major deviations individually and decide which subjects to exlude from PP population. The sponsor will provide a list of subjects to be excluded from PP population The sponsor review will be completed before DB lock..

9.3 Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be completed for the ITT population. Baseline summaries will be presented overall, by treatment group (as randomized) and for the two subgroups “AAD only within Control Group” amd “Cross-over within Control Group”.

Descriptive summaries of demographic and other baseline conditions will include:

- Demographics (Age, Gender) (ITT)

  Imbalances between treatment groups will be tested by a Wilcoxon rank sum test for age and a Fisher test for gender.

- Cardiovascular Medical History (ITT Population) including
  - Lone AF
  - Reversible AF
  - Previously diagnosed with persistent/permanent AF/AT
  - Previously required cardioversion >48 hours after onset of AF/AT
  - Heart disease (including history of angina, congestive heart failure, hypertension, ischemic cardio-myopathy, non-ischemic

dilated cardio-myopathy, hypertrophic obstructive cardio-myopathy, significant valve disease, valve replacement/surgery, congenital heart disease, left ventricular hypertrophy, myocardial infarction, Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Graft [CABG]), heart transplantation).

- Micro-/Thromboembolisms (by type of micro-/ thromboembolism)
- Other arrhythmia (by type of other arrhythmia)
- Hemorrhagic Stroke

- Other Medical History (significant pulmonary disease, obstructive lung disease, diabetes, hyperlipidemia/dyslipidemia, renal insufficiency, and dementia)
- Prior Procedures
- AF History (time since first experience of AF, number of episodes in the past 6 months and HATCH score)
- Cardiovascular medication history (Previously failed therapeutic strategies by generic drug name, historical maximum dose by generic drug name converting all doses to the same unit (mg))

9.4 Study Treatment

The study treatments will be summarized according to the following features:

- Number of subjects in Control group with crossover to a RF ablation
- First ablation procedure (index ablation procedure in test group)
  - Anticoagulation strategy
  - Catheter used
  - Ablation catheter inserted (Y/N)
  - RF ablation performed (Y/N)
  - Heart rhythm at start
  - PV ablation (Y/N)
  - RF energy delivery time
  - Ablation outcome (complete PVI achieved: Y/N, entrance block confirmed: Y/N, sinus rhythm at the end of the procedure: Y/N, electrical cardioversion at the end of the procedure: Y/N, sinus rhythm post electrical cardioversion: Y/N)
- Baseline Medication regimen (same as pre-study, new) (drug therapy group only)
- Cardiovascular Medication (see below)

Summaries of Cardiovascular Medication: Cardiovascular Medication will be coded using the WHO Drug Dictionary (September 2011 or newer). Incidences of cardiovascular medications will be summarized by ATC level 2 and ATC level 4, if

applicable, and by treatment group, unless otherwise specified. The following summaries of incidences will be prepared including test and control group:

- Cardiovascular medication at baseline: All cardiovascular medication which was started before/at date of randomization and was not discontinued before/at date of randomization will be included in this summary.
- Cardiovascular medication started after baseline: All cardiovascular medication which was started after date of randomization will be included in this summary. This may include dose changes after baseline if these are recorded as new medication entries.
- Concomitant cardiovascular medication: All cardiovascular medication which was started at any time during study and was not discontinued before/at date of randomization will be included in this summary.

In case start and/or end date are incomplete, a medication will be analyzed as concomitant medication as long as it cannot definitely be shown that the medication was discontinued before date of randomization. For concomitant medications, in case it cannot unequivocally be decided if the medication started before or after baseline, these will be analyzed as baseline medication, but excluded from medication started after baseline.
Additionally to these general medication summaries, summaries of new AADs started after baseline will be prepared as described in section 10.6.2).

10. EFFICACY ANALYSIS

Formal planned analyses are described below. It may be necessary for additional exploratory analyses to be completed in this study after results from the planned analysis are completed. Full details of additional analyses will be given in the CSR.

10.1 Primary Efficacy Variable Analysis

The primary analysis will be a Kaplan-Meier (KM) analysis for all subjects in the ITT population and account for censored observations. The primary effectiveness analysis will be performed in the ITT population, where the subjects will be attributed to the treatment group as randomized, regardless of treatment cross-over or post-randomization medical care. A log-rank test will be used to compare the hazard functions between the two groups at any observed event time. If observed, the median time to persistent AF/AT as well as the 95% confidence intervals will be reported by treatment group based on Kaplan-Meier estimates. The rate of survival without persistent AF/AT and rate of persistent AF/AT at 3 years follow-up as well as the 95% confidence intervals for both groups will be presented using the product limit estimate from the Kaplan Meier curve. Kaplan-Meier curves will be plotted.
The effect size is defined as the negative log of the hazard ratio (hazard rate of the Test Group over hazard rate of the Control Group): $\delta = -\log_e(\lambda_t/\lambda_c)$.
This study is to test the following hypothesis using a one-sided test at alpha equal to 0.025:

H0: $\delta \leq 0$

H1: $\delta > 0$

Null hypothesis: the hazard rate in the Test Group is greater than or equal to the hazard rate in the Control Group at observed event times during the follow-up period

Alternative hypothesis: the hazard rate in the Test Group is less than the hazard rate in the Control group at observed event times during the follow-up period

Subjects will be considered to have an effectiveness success if they do not progress to persistent AF/AT through the 3-year follow-up period.

10.2 PP analysis

The Kaplan-Meier analysis as described in section 10.1 will be repeated in the PP population (based on the as-treated principle).

Moreover, an inferential analysis using a Cox proportional hazards model will be performed in the PP subject population. For the Cox proportional hazards model, treatment itself will be modelled as a time-dependent covariate, i.e:

- for control group (without cross-over): treatment at time t is "control" at any time t
- for ablation group (without cross-over): treatment at time t is "ablation" at any time t
- for cross-over group: treatment at time t is control at any time t before cross-over and ablation at any time t after cross-over

The Cox proportional hazards model will be used to compare the hazard rate between the two treatment groups at observed event times.

The hazard ratio and its 95% confidence interval will be reported. Missing primary effectiveness endpoint data will be censored at the time of the subject's last visit/TTM.

The same principles outlined for section 10.1also apply for section 10.2(PP analysis).

10.3 Subgroup Analysis

The primary effectiveness analysis (KM analysis of time to persistent AF/AT) will be performed for the Test Group as randomized and for the Control Group as randomized (excluding cross-over subjects). The cross-over subjects (i.e., continued on their current AAD or taking a newly prescribed AAD and had an RF ablation procedure) will be analyzed separately as a third group.

- Test Group: randomized to RF ablation to achieve PVI using the CARTO® 3, CARTO® XP or CARTO® RMT System, and THERMOCOOL® Catheter Family

- Control Group: randomized to AAD therapy in accordance with current AF management guidelines[1-3]
- Cross-over Group: Control Group subjects who undergo RF ablation to achieve PVI using the CARTO® 3, CARTO ® XP or CARTO® RMT System, and THERMOCOOL® Catheter Family

If observed, the median time to persistent AF/AT as well as the 95% confidence intervals will be reported for the three groups based on Kaplan-Meier estimates. Kaplan-Meier curves will be plotted. The product limit estimates of the rate of survival without persistent AF/AT and rate of persistent AF/AT at 3 years follow-up as well as the 95% confidence intervals for these three groups will be presented separately.

10.4 Interim Analysis

To properly account for the repeated interim testing in this study, a group sequential method similar to that proposed by O'Brien and Fleming as a guide in interpreting interim analyses will be used.[7] This procedure requires large critical values early in the study, but relaxes (i.e., decreases) the critical value as the trial progresses. Because of the conservatism early in the trial, the critical value at the final analysis is near the "nominal" critical value. Hence, the sample size requirements with this group sequential procedure remain essentially the same as the conventional fixed sample size estimate. The actual method for the interim reporting that will be employed in this study is the “alpha-spending function” approach to group sequential testing developed by Lan and DeMets.[8] The Lan-DeMets approach is flexible to accommodate unequal sized groups with the number of interim looks unspecified in advance. It only requires specification of the rate at which the Type I error (which in this trial will be α=0.025 for the primary endpoint) will be "spent". This procedure allows "spending" a portion of α at each interim analysis in such a way that at the end of the study, the total Type I error does not exceed 0.025. This spending function generates boundaries that are nearly identical to the O'Brien-Fleming boundaries.

In survival trials, information time is calculated based upon number of events rather than number of subjects accrued. In practice, interim analyses are often scheduled based upon specified calendar time rather than number of events. To address the logistical inconvenience, Lan and DeMets extended their general group sequential approach for the maximum duration trial.[9] That is, the conduct of a trial is expected to occur within some period of time [0, Tc], where Tc is the maximum calendar (or duration) time for completion. The stopping boundaries can be adjusted based on the actual number of events observed at the interim look, rather than information fraction. This method allows flexibility in the monitoring process for accommodating any changes in terms of timing and spacing of the looks or additional examination of the data that is not pre-determined in response to the concerns from the GSMC that may arise during the course of the trial.

The analytic approach that will be used for the interim analyses for assessing treatment differences will be the time-to-event analysis method. The standardized log rank score statistic will be compared with the stopping boundaries at each interim look to draw statistical inference. If the stopping boundary is crossed, then the study

will stop for effectiveness.

Judgment concerning the continuation or termination of the study will involve not only the degree of statistical significance observed at the interim analysis, but also the likelihood of achieving significance should enrollment continue to the originally projected sample size. As an aid in this latter assessment, the group sequential analyses outlined above will be supplemented with calculations of conditional power. Conditional power (CP) for the primary treatment comparison will be provided to the GSMC as a regular part of the interim study reports. If the CP is less than 0.3, then the study will be stopped for futility.

The time points of the interim analyses and the number of interim analyses are not fixed in advance. The table below contains an example, based on initially estimated study times. The example assumes a first interim analysis after 12 months and then interim looks every half a year. For example, the anticipated start time for this study is December, 2012 and the expected end of subject enrollment is June, 2014. With 3 years follow-up time, the study is expected to be completed in June, 2017. Interim looks are planned for December 2013, June 2014, December 2014, June 2015, December 2015, June 2016, and December 2016, with a final look in June 2017. The stopping boundaries for effectiveness for these scheduled looks are displayed in the table below. At the time point of each interim analysis, the operating characteristics will be recalculated based upon the actual information fractions for the interim analyses already conducted and proportionally adjusted information fractions for all future interim analyses following methods described by Proschan, Lan and Wittes [10]. The software WinLD will be used. The approach implemented in the software WinLD takes into account calendar time as well as number of events. Calendar time scale will be used for the spending function. Number of events will be used to estimate covariance. At the time point of each interim analysis, boundaries will be re-estimated based on updated current calendar time estimate and actual number of events for all interim analyses up to the corresponding time point. The current calendar time estimate will be updated based on actual time point of current interim analysis, but using the maximum duration estimated at the time point of first interim analysis, thus previous estimates of calendar time will not change.

Operating Characteristics for Group Sequential Design

Look #	Intended Time after study start	Information Fraction	Number of Events	Stopping Bounds	Incremental Alpha	Cumulative Alpha
1	12 months	0.22	5	4.6374	0.00000	0.00000
2	18 months	0.33	9	3.7332	0.00009	0.00010
3	24 months	0.44	11	3.1913	0.00063	0.00073
4	30 months	0.56	15	2.8277	0.00192	0.00265
5	36 months	0.67	20	2.5881	0.00341	0.00606
6	42 months	0.78	22	2.3477	0.00499	0.01105
7	48 months	0.89	26	2.2183	0.00639	0.01744
8	54 months	1	28	2.0507	0.00756	0.02500

At any interim monitoring time l_j, we compute the Z statistic at information fraction t_j using the standardized logrank score statistic:

$$Z(t_j) = \frac{S(l_j)}{\sqrt{V(l_j)}}$$

where $S(l_j)$ is the observed logrank score statistic at time l_j, and $V(l_j)$ is the variance of $S(l_j)$. These statistics will be calculated using SAS PROC LIFETEST.

The Z test statistic will be compared with the stopping boundaries to determine whether this study will be stopped for effectiveness in each of the interim analyses. If the Z statistic crosses the stopping boundary, that is, Z is greater than the critical value at the interim look, then the study will be stopped for effectiveness. If the sample size exceeds the pre-planned sample size, then the CHW (Down-Weight) adaptive method will be used for statistical testing[6] as detailed in section 6.

Conditional power will be calculated starting from first interim look to assist the determination of whether the study will be stopped for futility. SAS PROC SEQTEST will be used, with the expected effect size specified in section 6.

10.5 Sensitivity Analysis for the Primary Efficacy Variable

A sensitivity analysis will be performed using time to persistent AF (HRS 2017) as an alternative definition of the primary endpoint (see section 8.3). The analyses described in sections 10.1 to 10.3 will be repeated for this alternative definition. As this definition has not been investigated in any interim analysis, this sensitivity analysis will not need to be adjusted for interim looks. A one-sided alpha level of α=0.025 will be used.

10.6 Secondary Efficacy Variable Analysis

10.6.1 Rate and Time to Persistent AF/AT at 1 year and 2 years follow-up and at 3 years follow-up by number of ablations

For the secondary effectiveness endpoint, the rate and time to persistent AF/AT

(excluding isthmus dependent atrial flutter) at 1 year and 2 years, a KM analysis will be performed to examine the hazard function of persistent AF/AT (excluding isthmus dependent atrial flutter) for the two treatment groups at 1 year follow-up time and 2 year follow-up. Data will be censored at 1 year and 2 year follow-up (for subjects who are not censored earlier) in two separate analyses. The analyses will be performed on both the ITT and PP populations. Log-rank tests will be used to compare the hazard functions between the two groups at any observed event time. If observed, the median time to persistent AF/AT at 1 year and 2 year follow-up as well as the 95% confidence intervals will be reported by the two groups based on Kaplan-Meier estimates. The product limit estimates of the rate of survival without persistent AF/AT and the rate of persistent AF/AT at 1 year and 2 years follow-up as well as the 95% confidence intervals for the rates in the two groups will be presented.

A KM analysis will also be performed to examine the hazard function of persistent AF/AT (excluding isthmus dependent atrial flutter) at 3 years by number of ablations for the Test group. Number of ablations will be categorized into 1, 2, ≥ 3 ablations if sample sizes allow (otherwise, only categories for 1 and ≥2 ablations will be used). The median time to persistent AF/AT at 3 years follow-up as well as the 95% confidence intervals will be reported for the Test Group by the number of ablations. The product limit estimates of the rate of survival without persistent AF/AT and the rate of persistent AF/AT at 3 years follow-up as well as the 95% confidence intervals for the Test Group will also be presented by the number of ablations. The KM curves will be plotted and results will be listed as well.

These secondary efficacy variable analyses will also be repeated using the alternative definition of time to persistent AF (HRS 2017), as defined in section 8.3.

10.6.2 Number of Repeat Ablations and New AAD Drugs

To analyze this secondary effectiveness endpoint (number of repeat ablations and new AAD drugs per subject throughout 3 years follow-up), the number of repeat ablations will be summarized and listed for the subjects who have undergone at least one ablation. In addition, new AAD use (number of new AAD drugs per subject) and the frequency of dose changes will be summarized and listed for all subjects by treatment group. A new AAD will be defined as an AAD (class I or class III, or AV nodal blocking agents such as beta blockers (BB) and calcium channel blockers (CCB), which was started after randomization and which was not administered at baseline (i.e there is no AAD entry with the same preferred term at baseline). The analyses will be performed on both ITT and PP populations. All medications will be coded by using the World Health Organization Drug Dictionary (September 2011 or newer) for this study. The number and percentage of subjects taking new AAD medications will be summarized by ATC level 2 and ATC level 4, overall and by treatment for the ITT and PP population.

10.6.3 Rhythm throughout 3 Years Follow-up

For this secondary endpoint, the following definition will be used:

- % subjects in sinus rhythm at a specific visit: This variable will refer to the data captured at the visit. Details will be defined when preparing analysis programs.
- % subjects with recurrent AF/AT at a specific visit: This variable will also refer to the time period after previous visit up the visit analyzed (including data captured at the visit analyzed). A subject has recurrent AF/AT if AF or AT is documented at any TTM, Holter or ECG within this timeframe (additional observations of any other rhythms at the same TTM; Holter or ECG are allowed).

To analyze this secondary effectiveness endpoint, rhythm (% subjects in sinus rhythm, % subjects with recurrent AF/AT) throughout 3 years follow-up, the number of subjects and percentage of subjects in sinus rhythm and the number and percentage of subjects with recurrent AF/AT at each visit during the 3 year follow-up time will be summarized and listed by treatment group at each follow-up visit. The analyses will be performed in both ITT and PP populations. Cross-over subjects will be completely excluded in the PP population.

10.6.4 Factors Associated with AF Disease Progression

To analyze this secondary endpoint, conditions that may be associated with disease progression will be assessed at baseline and throughout the 3-year follow-up period.

Cox proportional hazards models will be used to examine the associations of baseline-variables with time to disease progression. Time to disease progression is referring to time to persistent AF/AT (primary endpoint) in this section. The following baseline variables will be investigated:

- gender
- age (categories: <75 years, >=75 years)
- LA size (Parasternal long axis view from transthoracic echocardiogram) (not large: <= 55mm/large: >55mm)
- AF duration (continuous)
- number of AF events in 6 months prior to trial
- heart failure (yes vs. no) (as specified in HATCH score component)
- hypertension (yes [past or present] vs. no)
- hyperlipidemia/dyslipidemia (yes [past or present] vs. no)
- renal insufficiency (yes [past or present] vs. no)
- diabetes (yes vs. no)
- dementia (yes vs. no)
- previous TIA or stroke (yes vs. no) (as specified in HATCH score component)
- previous COPD (yes vs. no)(as specified in HATCH score component)

For the baseline variables, in a first step, single covariate Cox models including the

respective covariate, the treatment factor and the covariate*treatment interaction term will be fitted. In a second step, a multivariate Cox model will be fitted including the treatment factor and all covariates plus covariate*treatment interaction terms for which either the covariate or the interaction term had been associated with time to disease progression with a p-value < 0.2 in the single variate model. The Stepwise option of PROC PHREG will be used for model selection, setting the level for covariates to enter and to stay in the model to 0.05.

These analyses will be performed in the ITT and PP populations (with fixed treatment effect in the PP population).

Moreover, in the PP population the following analysis will be performed modelling the treatment effect as time-dependent covariate and additionally including baseline covariates: in a first step, single covariate Cox models including the respective covariate and the treatment factor (as time-dependent covariate) will be fitted. In a second step, a multivariate Cox model will be fitted including the treatment factor (as time-dependent covariate) and all covariates which had been associated with time to disease progression with a p-value < 0.2 in the single variate model. The Stepwise option of PROC PHREG will be used for model selection, setting the level for covariates to enter and to stay in the model to 0.05.

11. SAFETY AND TOLERABILITY ANALYSES

All safety end points will be presented by using the safety population.

11.1 Adverse Events

An overall summary of AEs will be presented and will include the number and percentages of subjects with

- any adverse events
- catheter-related adverse events
- procedure related adverse events
- study drug related adverse events
- primary adverse events
- serious adverse events
- adverse events leading to withdrawal

All adverse events will be coded using MedDRA coding dictionary.

Summaries of incidence rates of individual AE (number and percentage of subjects) by MedDRA system organ class and preferred term will be prepared.

Such summaries will be displayed for all AE, AE by maximum severity and AE by strongest causality to catheter, procedure or study drugs.

In these summaries, each subject will be counted only once within each category. If a subject experiences more than one AE within a category, only the AE with the strongest causality or the maximum severity, as appropriate, will be included in the summaries by causality and severity.

11.2 Catheter-related complications (AEs)

A key secondary safety endpoint, catheter-related complications (AEs), is limited to subjects who have initiated RF ablation and who are in the safety population. Catheter-related AEs are those AEs that are identified as possibly, probably or definitely related to the study device. The number and percentage of subjects with catheter-related AEs will be summarized by system organ class and perferred term for Test Group and cross-over subjects and overall in the safety population. Moreover, catheter-related complications will be summarized (overall, all types accumulated), in a further table containing the number and percentage of subjects with catheter-related complications by number of repeat ablations, by anticipated or not, by severity and by outcome.

11.3 Serious AEs

The number and percentage of subjects with SAEs will be summarized by system organ class and preferred term for both treatment groups and overall and in a further table by causality and by severity.

The summary by AE category will also be prepared for serious catheter-related AEs and serious catheter-related AEs by timeframe. Three timeframes will be included in this summary: acute phase AEs (ablation to $\leq$ 7 days) and sub-chronic AEs (>7 to 30 days post ablation), and chronic AEs (occuring more than 30 days post ablation).

11.4 Primary AEs

Primary AEs are defined as specific AEs that occur within 7 days of ablation procedure (AE categories as defined in the study protocol).

The number and percentage of subjects with primary AEs will be summarized by system organ class and preferred term, overall and by treatment group.

11.5 Adverse Drug Reactions

The number and percentage of subjects with adverse drug reactions defined as AE possibly, probably or definitely related to AAD will be summarized by system organ class and preferred term according to Test Group, cross-over group and Control Group (without cross-over subjects). The number and percentage of subjects with adverse drug reactions will also be summarized by causality, by anticipated or not, by severity and by outcome.

12. OTHER PLANNED ANALYSES

12.1 Quality of Life Analysis

Quality of Life (QoL) is assessed using the EQ-5D and AFEQT questionnaires. Quality of Life (QoL) status will be compared to baseline at 3 months, 6 months, 1 year, 2 years and 3 years. Descriptive statistics for the baseline and absolute values as well as changes from baseline of the scores (AFEQT overall score, AFEQT symptoms score, AFEQT daily activity score, AFEQT treatment concern score, AFEQT treatment satisfaction score, EQ-5D VAS)) at follow-up visits will be summarized by treatment groups. The analyses will be performed in the PP population. Cross-over subjects will be completely excluded for all QoL summaries.

Paired-sample t-tests will be used to test whether the change-from-baseline values differs from zero within each treatment group. A two-sample comparison of the two groups with respect to changes-from-baseline in QoL will be performed using a repeated measurement model, including the baseline value as a covariate and assessing treatment group differences. EQ-5D single items will be summarized descriptively in a frequency table by treatment group for baseline and follow-up visits. Changes from baseline in EQ-5D single items will also be presented for each follow-up visit in a frequency table. It will then be tested if there is a difference between test and control group using Wilcoxon-Mann-Whitney test separately for each follow up visit.

12.2 Health Economics Analysis

For this secondary health economic endpoint, health care utilization (number and length of hospitalizations and unscheduled cardiovascular-related visits), the total number and length of hospitalizations will be summarized by treatment groups in the ITT population.

13. REPORTING CONVENTIONS

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations.

13.1 General Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation, unless presented as part of the text in a CSR.
- Figures will be presented in Landscape Orientation, unless presented as part of the text in a CSR.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be in black and white, unless color figures have been identified as useful for discriminating presentation in the figure. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table,

figure, or data listing. Hexadecimal character representations are allowed (e.g., μ, α, β).

- All titles will be centered on a page. The ICH numbering convention is to be used for all TLGs.
- All footnotes will be left justified and the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as DDMMMYYYY (e.g., 29AUG2001) format. A four-digit year is preferred for all dates.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.
- Time durations will be reported in HH:MM:SS notation. The use of decimal notation to present (display) time durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figure, and data listings will have the name of the program, programmer, and a date stamp on the bottom of each output.

13.2 Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as “Population: <name of population>” and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population. Common nomenclature may include (a) Full Analysis or ITT, (b) All Subjects, (c) PP or Per-Protocol, (d) Efficacy, (e) Safety, or (f) Pharmacokinetic.
- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., ITT

Females, Per-Protocol Males >60 years of age) used for analysis in a table or figure.

- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of subjects with non-missing values.
- All population summaries for continuous variables will include: N, mean, SD, minimum, and maximum. Other summaries (e.g. number missing, median, quartiles, 5%, 95% intervals, CV or %CV) may be used as appropriate.
- All percentages are rounded and reported to a single decimal point (xx.x%).
- Population summaries that include p-values will report the p-value to three decimal places with a leading zero (0.001). All p-values reported on default output from statistical software (i.e., SAS® Software) may be reported at the default level of precision. P-values <0.001 should be reported as <0.001 not 0.000.

14. REFERENCES

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15. TABLES, LISTINGS, AND FIGURES

15.1 Planned Table Descriptions

The following are planned summary tables for protocol 144 (09-Apr-2013). Tables will be numbered according to the nomenclature used to support the clinical study report.

Tables will be split according to population adding an additional table extension digit.

It is indicated in the last column which tables will be also produced for interim analysis. All tables, where an interim analysis number is specified, will be included in the interim analysis.

Table Number	Population	Table Title / Summary	Sup-porting Listing	Interim Analysis Number
14.1 DEMOGRAPHIC DATA				
14.1.1.1.1	ITT	Study Subjects Analysis Populations	16.2.1	1.1 ITT and safety set only
14.1.1.1.2	ITT	Study Subjects Distribution of Subjects by Site	16.2.1	
14.1.1.2	ITT	Study Subjects Disposition	16.2.3	1.2
14.1.1.3	ITT	Study Subjects Reasons for Withdrawals	16.2.3	
14.1.1.4	ITT	Study Subjects Protocol Deviations Reported in CRF by Protocol Deviation Code	16.2.4.2	
14.1.2	ITT	Demographics Age and Sex	16.2.6	
14.1.3.1	ITT	Cardiovascular History Lone and Reversible AF, Previously Persistent/ Permanent AF/AT,	16.2.7	

Table Number	Population	Table Title / Summary	Sup-porting Listing	Interim Analysis Number
		Previously Required Cardioversion		
14.1.3.2	ITT	Cardiovascular History Heart Disease	16.2.7	
14.1.3.3	ITT	Cardiovascular History Micro-/ Thromboembolism	16.2.7	
14.1.3.4	ITT	Cardiovascular History Other Arrhythmia	16.2.7	
14.1.3.5	ITT	Cardiovascular History Hemorrhagic Stroke	16.2.7	
14.1.4.1	ITT	Other Medical History	16.2.8	
14.1.4.2	ITT	Prior Procedures	16.2.9	
14.1.5	ITT	AF History	16.2.10	
14.1.6.1	ITT	Cardiovascular Medication History Previously failed therapeutic strategies	16.2.11	
14.1.6.2	ITT	Cardiovascular Medication History Historical Maximum Dose by Generic Drug Name	16.2.11	
14.1.7.1	Safety	Study Treatment Overview Number of subjects in Control group with crossover to a RF ablation	16.2.1	
14.1.8.1	Safety	Study Treatment –Index Ablation Procedure Anticoagulation strategy	16.2.15	
14.1.8.2	Safety	Study Treatment – Index Ablation Procedure	16.2.15	

Table Number	Population	Table Title / Summary	Sup-porting Listing	Interim Analysis Number
		Name of catheters used		
14.1.8.3.1	Safety	Study Treatment - Index Ablation Procedure Procedural data	16.2.15	
14.1.8.3.2	Safety	Study Treatment - Index Ablation Procedure THERMOCOOL ® Catheter Specific Data	16.2.15	
14.1.8.4	Safety	Study Treatment – Index Ablation Procedure Ablation outcome	16.2.15	
14.1.9	ITT	Baseline Medication Regimen	16.2.16	
14.1.10.1	ITT	Cardiovascular Medication at Baseline	16.2.22	
14.1.10.2	ITT	Cardiovascular Medication started after Baseline	16.2.22	
14.1.10.3	ITT	Concomitant Cardiovascular Medication	16.2.22	

Table Number	Populatio n	Table Title / Summary	Sup-porting Listing	Interim Analysis Number
14.2 EFFICACY DATA				
14.2.1.1	ITT	Time to Persistent AF/AT (Primary Efficacy Analysis) Results of Kaplan-Meier analysis and log rank test	16.2.17.1	2.1 (but without rates at 3 years and incl. conditional power)
14.2.1.2	ITT	Time to Persistent AF/AT (Primary Efficacy Variable)	16.2.17.1	2.2

Table Number	Population	Table Title / Summary	Sup-porting Listing	Interim Analysis Number
		Recalculated Operating Characteristics for Group Sequential Design		
	ITT	Time to Persistent AF/AT (Primary Efficacy Variable) Sample Size Re-Estimation	16.2.17.1	2.3 Only required for first interim analysis; not required for final analysis
14.2.1.3	ITT	Time to Persistent AF (HRS 2017) Results of Kaplan-Meier analysis and log rank test	16.2.17.1	
14.2.2.1	PP	Time to Persistent AF/AT Results of Kaplan-Meier analysis and log rank test	16.2.17.1	
14.2.2.2	PP	Time to Persistent AF/AT Cox regression analysis including treatment as time-dependent covariate	16.2.17.1	
14.2.2.3	PP	Time to Persistent AF (HRS 2017) Results of Kaplan-Meier analysis and log rank test	16.2.17.1	
14.2.2.4	PP	Time to Persistent AF (HRS 2017) Cox regression analysis including treatment as time-dependent covariate	16.2.17.1	
14.2.3.1	ITT	Time to Persistent AF/AT: Subgroup analyses Results of Kaplan-Meier	16.2.17.1	

Table Number	Population	Table Title / Summary	Sup-porting Listing	Interim Analysis Number
		analysis		
14.2.3.2	ITT	Time to Persistent AF (HRS 2017): Subgroup analyses Results of Kaplan-Meier analysis	16.2.17.1	
14.2.4.1	ITT, PP	Time to Persistent AF/AT by Number of Repeat ablations Results of Kaplan-Meier analysis	16.2.17.1	
14.2.4.2	ITT, PP	Time to Persistent AF/AT at 1 Year Results of Kaplan-Meier analysis and log rank test	16.2.17.1	
14.2.4.3	ITT, PP	Time to Persistent AF/AT at 2 Years Results of Kaplan-Meier analysis and log rank test	16.2.17.1	
14.2.4.4	ITT, PP	Time to Persistent AF (HRS 2017) by Number of Repeat ablations Results of Kaplan-Meier analysis	16.2.17.1	
14.2.4.5	ITT, PP	Time to Persistent AF (HRS 2017) at 1 Year Results of Kaplan-Meier analysis and log rank test	16.2.17.1	
14.2.4.6	ITT, PP	Time to Persistent AF (HRS 2017) at 2 Years Results of Kaplan-Meier analysis and log rank test	16.2.17.1	
14.2.5	ITT, PP	Number of Repeat Ablations	16.2.17.3	

Table Number	Population	Table Title / Summary	Sup-porting Listing	Interim Analysis Number
14.2.6	ITT, PP	Number of New AAD Drugs per Subject	16.2.17.3	
14.2.7	ITT, PP	Summary of Dose changes	16.2.22	
14.2.8	ITT, PP	New AAD Drugs – ATC classes	16.2.22	
14.2.9	ITT, PP	Heart Rhythm	16.2.17.3	
14.2.10.1	ITT, PP	Factors Associated With Time to Persistent AF/AT Results of Cox models with single baseline covariates	16.2.17.1	
14.2.10.2	ITT, PP	Factors Associated With Time to Persistent AF/AT Results of Cox model with multivariate baseline covariates	16.2.17.1	
14.2.10.3	PP	Factors Associated With Time to Persistent AF/AT Results of Cox models with single baseline covariates and treatment as time-dependent covariate	16.2.17.1	
14.2.10.4	PP	Factors Associated With Time to Persistent AF/AT Results of Cox model with multivariate baseline covariates and treatment as time-dependent covariate	16.2.17.1	
14.2.11.1	PP	Quality of Life – EQ5D Descriptive summary of VAS	16.2.14	
14.2.112	PP	Quality of Life – EQ5D	16.2.14	

Table Number	Population	Table Title / Summary	Sup-porting Listing	Interim Analysis Number
		Descriptive summary of changes from baseline in VAS		
14.2.11.3	PP	Quality of Life – EQ5D Results of repeated measurement model for changes from baseline in VAS	16.2.14	
14.2.11.4	PP	Quality of Life – EQ5D Frequency table for EQ-5D single items	16.2.14	
14.2.11.5	PP	Quality of Life – EQ5D Frequency table for changes from baseline in EQ-5D single items and results of Wilcoxon-Mann-Whitney test	16.2.14	
14.2.12.1	PP	Quality of Life – AFEQT Descriptive summary of derived scores	16.2.13	
14.2.12.2	PP	Quality of Life – AFEQT Descriptive summary of changes from baseline	16.2.13	
14.2.12.3	PP	Quality of Life – AFEQT Results of repeated measurement model	16.2.13	
14.2.13.1	ITT	Health Economic Analysis Number of hospitalizations	16.2.25	
14.2.13.2	ITT	Health Economic Analysis Length of hospitalizations	16.2.25	
14.2.13.3	ITT	Health Economic Analysis	16.2.25	

Table Number	Population	Table Title / Summary	Sup-porting Listing	Interim Analysis Number
		Number of unscheduled cardiovascular-related visits		
14.3 SAFETY DATA				
14.3.1	Safety	Adverse Events Summary Table	16.2.23	
14.3.2	Safety	Adverse Events by System Organ Class and Preferred Term	16.2.23	
14.3.3.1	Safety	Adverse Events by System Organ Class and Preferred Term and Maximum Severity of Event	16.2.23	
14.3.3.2	Safety	Adverse Events by System Organ Class and Preferred Term and Strongest Causality to Study Device	16.2.23	
14.3.3.3	Safety	Adverse Events by System Organ Class and Preferred Term and Strongest Causality to Study Procedure	16.2.23	
14.3.3.4	Safety	Adverse Events by System Organ Class and Preferred Term and Strongest Causality to Study Drugs	16.2.23	
14.3.4.1	Safety	Catheter-Related Adverse Events by System Organ Class and Preferred Term	16.2.23	
14.3.4.2	Safety	Catheter-Related Adverse Events by Number of Repeat Ablations, by Anticipated or not, by Severity and by Outcome	16.2.23	

Table Number	Population	Table Title / Summary	Sup-porting Listing	Interim Analysis Number
14.3.4.3	Safety	Catheter Related Adverse Events – Listing of Cases	16.2.23	
14.3.5.1	Safety	Serious Adverse Events by System Organ Class and Preferred Term	16.2.23	
14.3.5.2	Safety	Serious Adverse Events by Causality and by Severity	16.2.23	
14.3.5.3	Safety	Serious Catheter-Related Adverse Events by System Organ Class and Preferred Term	16.2.23	
14.3.5.4	Safety	Serious Catheter-Related Adverse Events by System Organ Class and Preferred Term and Time Frame	16.2.23	
14.3.5.5	Safety	Serious Adverse Events Listing of Cases	16.2.23	3.3
14.3.6.1	Safety	Primary Adverse Events by System Organ Class and Preferred Term	16.2.23	
14.3.6.2	Safety	Primary Adverse Events Listing of Cases	16.2.23	3.4
14.3.7.1	Safety	Adverse Drug Reactions by System Organ Class and Preferred Term	16.2.23	
14.3.7.2	Safety	Adverse Drug Reactions by Causality, by Anticipated or not, by Severity and by Outcome	16.2.23	
14.3.7.3	Safety	Adverse Drug Reactions Listing of Cases	16.2.23	

15.2 Planned Listing Descriptions

The following are planned data and subject listings for protocol 144 (09-Apr-2013). Listings will number according to the nomenclature used to support the clinical study report. Listings will be ordered by treatment group and subject and timepoint. In addition to the unique subject identification, the treatment group will be displayed on all listings.

It is indicated in the last column which listings will also be produced for interim analysis.

Listing Number	Population	Listing Title / Summary	Interim Analysis
16.2.1	All Subjects	Study Population Status for Each Subject	
16.2.2	ITT	Inclusion/Exclusion Criteria for Each Subject	
16.2.3	ITT	Study Completion Status and Discontinued Subjects	
16.2.4.1	Screening Failures	Reason for Screening Failures	
16.2.4.2	ITT	Protocol Deviations Reported in CRF	
16.2.4.3	ITT	Major Protocol Deviations and Exclusions from Analysis Populations	
16.2.5	ITT	Visit Dates Including Days since Randomization	
16.2.6	ITT	Subject Demographics	
16.2.7	ITT	Cardiovascular Medical History	
16.2.8	ITT	Other Relevant Medical History	
16.2.9	ITT	Prior Procedure History	
16.2.10	ITT	AF History	
16.2.11	ITT	Cardiovascular Medication History	
16.2.12	ITT	Screening Examination Done (Yes/No)	

Listing Number	Population	Listing Title / Summary	Interim Analysis
16.2.13	ITT	AFEQT Questionnaire	
16.2.14	ITT	EQ-5D Questionnaire	
16.2.15	ITT	Ablation Procedures	
16.2.16	ITT	Baseline Medication Optimization	
16.2.17.1	ITT	Primary Endpoint: Time to Persistent AF/AT	3.1
16.2.17.2	ITT	CEC Adjudication Form	
16.2.17.3	ITT	Secondary Endpoints - Number of repeat ablations and new anti-arrhythmic drugs and heart rhythm	
16.2.18	ITT	Follow-Up Visits – Assessments Performed	
16.2.19	ITT	Blood Pressure	
16.2.20	ITT	NYHA Classification and Additional Diagnoses	
16.2.21	ITT	HATCH Score	
16.2.22	ITT	Cardiovascular Medication	
16.2.23	ITT	Adverse Events	3.2
16.2.24	ITT	Serious Adverse Events Form	
16.2.25	ITT	Unscheduled Cardiovascular Visit/Hospitalization	
16.2.26	ITT	12-Lead ECG	
16.2.27	ITT	Holter Monitoring	
16.2.28	ITT	Event Recorder	
16.2.29	ITT	Transesophageal Echocardiogram	
16.2.30	ITT	Transthoracic Echocardiogram	
16.2.31	ITT	Cardioversion	

Listing Number	Population	Listing Title / Summary	Interim Analysis
16.2.32	ITT	Medication Management	

15.3 Planned Figure Descriptions

The following are planned summary figure for protocol 144 (09-Apr-2013). Figures will be numbered according to the nomenclature used to support the clinical study report.

It is indicated in the last column which figures will be also produced for interim analysis.

Figure Number	Population	Figure Title / Summary	Supporting Listing Number	Interim Analysis
14.5.1	ITT/PP	Time to Persistent AF/AT (Primary Efficacy Analysis) Kaplan Meier Curves	16.2.17.1	
14.5.2	ITT	Time to Persistent AF/AT - Subgroup Analysis Kaplan Meier Curves	16.2.17.1	
14.5.3	ITT/PP	Time to Persistent AF/AT by Number of Ablations Kaplan Meier Curves	16.2.17.1	
14.5.4	ITT/PP	Time to Persistent AF (HRS 2017) Kaplan Meier Curves	16.2.17.1	
14.5.5	ITT	Time to Persistent AF (HRS 2017) - Subgroup Analysis Kaplan Meier Curves	16.2.17.1	
14.5.6	ITT/PP	Time to Persistent AF (HRS 2017) by Number of Ablations Kaplan Meier Curves	16.2.17.1	