Montreal Health Innovations Coordinating Center
A Division of the Montreal Heart Institute

MHICC

STATISTICAL ANALYSIS PLAN

ADENOSINE FOLLOWING PULMONARY VEIN ISOLATION TO TARGET DORMANT CONDUCTION ELIMINATION

The ADVICE Trial

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Signature Approval Page

By signing below, I indicate that I have reviewed the Statistical Analysis Plan in its entirety and approve its contents.

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Revision History

Version	Date (DD-MMM-YYYY)	Author	Summary of Changes
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LIST OF ABBREVIATIONS

AE	Adverse Event
AF	Atrial Fibrillation
AFL	Atrial Flutter
ANOVA	Analysis of Variance
AT	Atrial Tachycardia
CRF	Case Report Form
ECG	Electrocardiogram
ITT	Intent To Treat
MHICC	Montreal Health Innovations Coordinating Center
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TEE	Transesophageal Echocardiogram
TTM	Trans-Telephonic Monitoring

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to present the statistical methodology that will be used for the analysis of the ADVICE trial. This plan also provides a description of the tables, figures and listings that will be included in the final statistical report. In case of differences between the SAP and the protocol, the SAP will supersede the protocol.

2 STUDY DESCRIPTION

2.1 Study Design

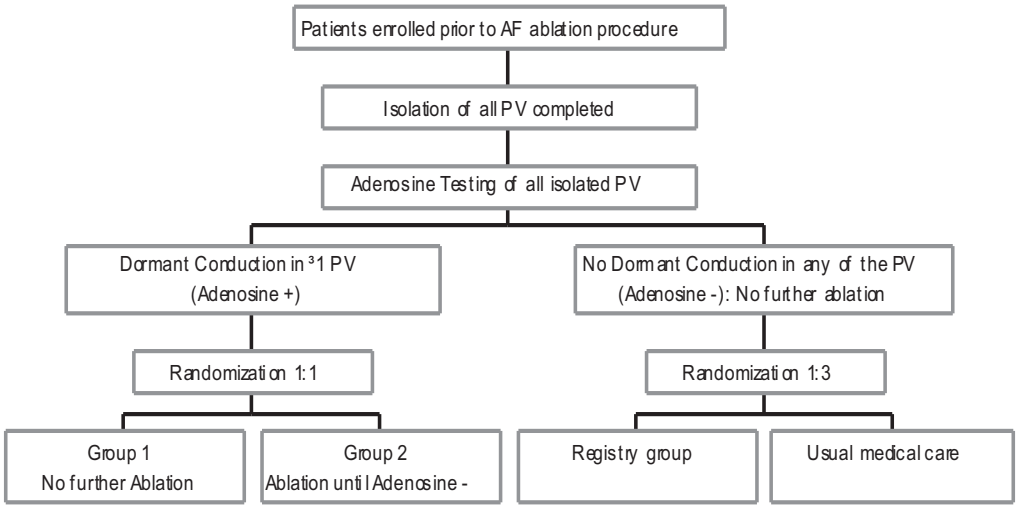
This is a prospective, open label, multi-centre, randomized trial in patients with paroxysmal atrial fibrillation (AF).Patients who meet the inclusion criteria will be enrolled in the study. After pulmonary vein isolation (PVI), dormant conduction between the pulmonary veins (PV) and the atrium will be evaluated using intravenous adenosine. If dormant conduction is present, the patients will be randomized in a 1:1 ratio to two parallel groups:

- Group 1: No additional ablation
- Group 2: Additional ablation until elimination of dormant conduction.

If no dormant conduction is documented, patients will be selected in a random fashion to be included in a registry (follow-up as planned for group 1 and 2 above). The registry group will allow for further assessment of the role of dormant conduction as a predictor of AF recurrence by comparing the success rate after ablation in patients without dormant conduction with those of Group 1 and 2.

Randomization will use blocks and will be stratified by site. The randomization schema is presented below.

Figure 1: Randomization schema



All patients randomized to group 1 or 2 or to the registry group will be evaluated according to the schedule below. For patients not included in the above 3 groups and who are assigned to usual medical care, data will be collected until discharge after the ablation procedure.

	Baseline	***Ablation***	**Discharge**	***Follow-up***		
	Day -30 to Day 0	Day 0	Day 1 to Day 4	3M	6M	12M
Consent	*X*					
Clinical examination	*X*	*X*	*X*	*X*	*X*	*X*
ECG	*X*	*X*	*X*	*X*	*X*	*X*
TTM (weekly)			*X*	*X*	*X*	*X*
24 H Holter				*X*	*X*	*X*
CT-Scan or MRI	*X*			*X*		
QoL	*X*			*X*	*X*	*X*

TTM: trans-telephonic monitoring, M: months

A maximum of 526 patients were to be enrolled into the study.

2.2 Study Objectives

The general aim of the project is to evaluate, in a randomized fashion, the efficacy of elimination of dormant pulmonary vein conduction using adenosine during PVI, to prevent recurrence of symptomatic AF after a single ablation procedure in patients with paroxysmal AF.

The primary objective is to compare the time to recurrence of symptomatic AF or atrial flutter/tachycardia in two groups after a single ablation procedure:

- Group 1: Presence of dormant PV conduction, no additional ablation
- Group 2: Presence of dormant PV conduction, additional targeted ablation until elimination of dormant conduction.

The secondary objectives include the evaluation of:

- Time to any recurrence of AF or atrial flutter/tachycardia (symptomatic or asymptomatic) in Group 1 vs. Group 2
- Time to recurrence of AF or atrial flutter/tachycardia in patients with absence of dormant conduction after PVI (registry patients) vs. Group 1. This analysis will be performed for symptomatic recurrences as well as for all recurrences (symptomatic or asymptomatic).
- Time to recurrence of AF or atrial flutter/tachycardia in registry patients vs. Group 2. This analysis will be performed for symptomatic recurrences as well as for all recurrences (symptomatic or asymptomatic).
- The need for repeat ablation procedures because of documented recurrence of symptomatic AF or atrial flutter/tachycardia.

- The need for emergency visits, hospitalizations or cardioversions.
- The evaluation of quality of life (QoL)
- Episodes of AF or atrial flutter/tachycardia during a blanking period of 3 months immediately following the ablation.
- Incidence of peri-procedural complications including stroke, PV stenosis, cardiac perforation, atrio-esophageal fistulae, and death.
- Procedure, radio frequency energy delivery time and fluoroscopy times.

A tertiary objective is to conduct a cost-effectiveness analysis. Details of this analysis will be available later on in a separate document.

3 DATASETS ANALYZED

3.1 Intent-To-Treat (ITT) Population

The ITT population will consist of all randomized patients as recorded in CRF p. 18. In the ITT population, patients allocated to a treatment strategy group by randomization will be followed up, assessed and analyzed as members of that group irrespective of their compliance to the planned course of treatment. Patients randomized by error (ex. not meeting inclusion/exclusion criteria) will be reviewed and possibly removed from the ITT population.

3.2 Evaluable Population

The evaluable population will consist of patients of the ITT population, excluding patients with major deviations from the protocol. The list of patients to be excluded will be provided by the principal investigator.

3.3Started Procedure Population

The started procedure population will consist of all patients who started the procedure. All randomized patients will be included (CRF p. 18), along with patients who started the procedure, but were not randomized (list provided by the principal investigator).

4 EFFICACY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary endpoint will be the time to first recurrence of electrocardiographically documented symptomatic AF or atrial flutter (AFL)/ atrial tachycardia (AT) between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days. In other words, either an AF/AFL/AT between Day 91 and study completion or any repeat ablation procedure (CRF Re-Ablation Form) will qualify as a primary endpoint.

AF/AFL/AT will be considered to be present if it lasts 30 seconds or longer and is documented by 12 lead

ECG, surface ECG rhythm strips or TTM recordings. Symptoms associated with atrial tachyarrhythmias will also be reported. All documented episodes of recurrent atrial tachyarrhythmias will be adjudicated by a blinded group of investigators. Occurrence of electrocardiographically documented symptomatic AF/AFL/AT will be captured through a special AF database that will be maintained and updated on a day-to-day basis.

To qualify for the primary endpoint, the episode must occur between Day 91 and study completion (inclusive). Any episode occurring before Day 91or after study completion will not be considered in the calculation of the primary endpoint. For a given patient, study completion will be taken as the date of study completion reported on CRF p. 40.

Time zero will be randomization date (CRF p. 18) + 90 days. The first episode occurring at or after Day 91, but not after study completion, will be identified and time to event will be calculated as the difference between Day 90 and the date of this first episode. In patients with a repeat ablation procedure between randomization and Day 90, time to event will be set to 1. Patients with no episode between Day 91 and study completion will be censored at their date of study completion (CRF p. 40). This is summarized in the table below.

Definition of primary efficacy endpoint (symptomatic AF/AFL/AT + repeat ablation)

Event (failure)	=	Symptomatic AF/AFL/AT between Day 91 and Day SC (inclusive) OR Any repeat ablation procedure

Time to event	=	Date of first event[(a)] – Day 90	If symptomatic AF/AFL/AT or repeat ablation between Day 91 and Day SC (inclusive)
		1	If repeat ablation procedure between randomization and Day 90
Time to event		Day SC – Day 90	If no event

[(a)] Date of first event is the AF/AFL/AT date or the date of repeat ablation, whichever comes first.

Note: Day X = randomization date (CRF p. 18) + X days
Day SC = study completion date (CRF p. 40).

4.2 Secondary Efficacy Endpoints

The secondary endpoints will include:

1) Time to first recurrence of electrocardiographically documented symptomatic AF/AFL/AT between Day 91 and study completion OR antiarrhythmic drug use between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days.

   This endpoint is similar to the primary endpoint with an additional component for antiarrhythmic drug use, as summarized below.

Definition of secondary efficacy endpoint (symptomatic AF/AFL/AT + antiarrhythmic drug + repeat ablation)

Event (failure)	=	Symptomatic AF/AFL/AT between Day 91 and Day SC (inclusive) OR Antiarrhythmic drug use between Day 91 and Day SC (inclusive) OR Any repeat ablation procedure

Time to event	=	Date of first event[(a)] – Day 90	If symptomatic AF/AFL/AT or repeat ablation or antiarrhythmic drug use between Day 91 and Day SC (inclusive)
		1	If repeat ablation procedure between randomization and Day 90
Time to event		Day SC – Day 90	If no event

[(a)] Date of first event is the AF/AFL/AT date or the date of repeat ablation or the antiarrhythmic drug start date, whichever comes first. If the antiarrhythmic drug started before Day 91, time to event will be set to 1.

Note: Day X = randomization date (CRF p. 18) + X days
Day SC = study completion date (CRF p. 40).

The use and start date of antiarrhythmic drug will be reviewed by the principal investigator prior to database lock and a listing will be available to properly assess this endpoint.

2) Time to first recurrence of any electrocardiographically documented AF/AFL/AT(symptomatic or asymptomatic) between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days.

This endpoint will be derived in a fashion similar to the primary endpoint, but without the requirement related to being symptomatic.

Definition of primary efficacy endpoint (all AF/AFL/AT + repeat ablation)

Event (failure)	=	Any AF/AFL/AT (symptomatic or asymptomatic)between Day 91 and Day SC (inclusive) OR Any repeat ablation procedure

Time to event	=	Date of first event[(a)] – Day 90	If any AF/AFL/AT (symptomatic or asymptomatic) or repeat ablation between Day 91 and Day SC (inclusive)
		1	If repeat ablation procedure between randomization and Day 90
Time to event		Day SC – Day 90	If no event

[(a)] Date of first event is the AF/AFL/AT date or the date of repeat ablation, whichever comes first.

Note: Day X = randomization date (CRF p. 18) + X days
Day SC = study completion date (CRF p. 40).

3) Time to first recurrence of any electrocardiographically documented AF/AFL/AT (symptomatic or

asymptomatic) between Day 91 and study completion OR antiarrhythmic drug use between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days.

This endpoint is similar to the first secondary endpoint, but without the requirement related to being symptomatic.

Definition of secondary efficacy endpoint (all AF/AFL/AT + antiarrhythmic drug + repeat ablation)

Event (failure)	=	Any AF/AFL/AT (symptomatic or asymptomatic)between Day 91 and Day SC (inclusive) OR Antiarrhythmic drug use between Day 91 and Day SC (inclusive) OR Any repeat ablation procedure

Time to event	=	Date of first event[(a)] – Day 90	If any AF/AFL/AT (symptomatic or asymptomatic) or repeat ablation or antiarrhythmic drug use between Day 91 and Day SC (inclusive)
		1	If repeat ablation procedure between randomization and Day 90
Time to event		Day SC – Day 90	If no event

[(a)] Date of first event is the AF/AFL/AT date or the date of repeat ablation or the antiarrhythmic drug start date, whichever comes first. If the antiarrhythmic drug started before Day 91, time to event will be set to 1.

Note: Day X = randomization date (CRF p. 18) + X days
Day SC = study completion date (CRF p. 40).

4) AF burden.

AF burden will be defined for the period from Day 91 to study completion and will be computed as:

AF burden (symptomatic AF) = # of weeks with at least one symptomatic AF/AFL/AT / # of weeks of transmission x 100

AF burden (any AF) = # of weeks with at least one AF/AFL/AT (symptomatic or asymptomatic) / # of weeks of transmission x 100

5) The need for repeat ablation procedure because of documented recurrence of symptomatic AF or atrial flutter/tachycardia.

A patient will be considered has having a repeat ablation procedure if at least one Re-Ablation Form is reported in the CRF for that patient.

6) Proportion of patients with emergency visit, proportion of patients who were hospitalized and proportion of patients who needed a cardioversion after discharge.

This information will be collected in the Resource Utilization Form of the CRF at Day 90, Day 180 and Day 365 (CRF p. 27, 33 and 38). A patient will be considered has having gone to the emergency room at a given time point if the answer to the corresponding question is YES at that time point The same will be done to identify patients who were hospitalized and patients who needed a cardioversion.

7) Proportion of patient who needed antiarrhythmic drug because of documented recurrence of symptomatic AF or atrial flutter/tachycardia.

   Antiarrhythmic drug use is a component of the first and third secondary endpoint and as already mentioned above, the use and start date of antiarrhythmic drug will be reviewed by the principal investigator prior to database lock and a listing will be available to properly assess this endpoint.

8) Proportion of patients with symptomatic AF/AFL/AT and proportion of patients with any AF/AFL/AT (symptomatic or asymptomatic) occurring during the first three months post ablation.

9) Proportion of patients reporting symptomatic atrial arrhythmia, number and duration of episodes (as per patient's assessment) between ablation and discharge, between discharge and Day 90, between Day 90 and Day 180 as well as between Day 180 and Day 365.

   This information will be collected in the CRF.

10) Incidence of peri-procedural complications including stroke, PV stenosis, cardiac perforation, pericarditis, atrio-esophageal fistulae, vascular access complication and death.

    These endpoints will be collected in an external log that will be provided by the project manager of the study and adjudicated by an independent event committee.

11) Generic and disease specific quality of life. The MHICC will not be responsible for the analysis of the quality of life questionnaire.

5 PROCEDURES, EVENTS AND OTHER EXAMS ANALYSIS

5.1 Procedure Parameters

Various parameters will be collected in the CRF during the baseline procedure as well as during additional procedures when applicable, including parameters related to the standard pulmonary vein isolation, the evaluation of dormant conduction, the dose of adenosine used and the need for further ablation.

5.2 Concomitant Medication

Concomitant medications will be collected throughout the study, starting at baseline (study entry).

5.3 Adverse Events and Serious Adverse Events

An adverse event (AE) is defined as an untoward medical occurrence in a patient. Adverse events occurring during the study will be documented in dedicated "Adverse Event" forms. Those events will be classified by the investigators according to their seriousness, and whether they are study/procedure related. All events will be adjudicated by an independent event committee.

Serious adverse events (SAE) will be defined as death, life-threatening events, events causing functional disability, an event requiring or prolonging hospitalization, or any other event considered serious by an investigator.

5.4 Trans-Telephonic Monitor

Information regarding the use of trans-telephonic monitor will be collected at each study visit.

5.5 Other Exam Analysis

Several exams will be performed during the study.

Vital signs (heart rate and blood pressure) and a 12-lead ECG will be assessed at baseline, before the ablation, at discharge and at Day 90, Day 180 and Day 365. Height and weight will be collected at baseline only.

A physical examination will be done at baseline and a 24-hour Holter monitor exam will be performed at baseline, Day 90, Day 180 and Day 365. A transthoracic echocardiogram / nuclear exam will be performed at baseline and a CT/MRI exam will be done at baseline and Day 90. A transesophageal echocardiogram (TEE) exam will be done before the ablation.

5.6 Laboratory Parameters

Some laboratory parameters will be collected before the ablation.

6 Statistical Methodology

6.1 Statistical Considerations

Statistical analyses will be performed using SAS Version 9.2 or higher. Unless otherwise specified, all statistical tests will be two-sided and performed at a significance level of 0.05. No adjustment for multiple testing will be done.

Prior to all parametric analyses, basic assumptions will be checked and if they are violated, non parametric analyses or data transformation will be performed to confirm results from the parametric analyses.

Descriptive statistics will be presented for most study parameters. For continuous variables, N, mean, median, standard deviation, Q1, Q3, minimum and maximum will be presented. Number of patients and proportion will be presented for categorical variables.

Unless otherwise stated, no missing value will be imputed.

6.2 Study Patients

6.2.1 Patient Disposition

Number of randomized patients, number of randomized patients completing the study and reasons for discontinuation will be summarized overall and by treatment strategy group. This information will also be presented by study site. A listing of patient disposition will be provided.

6.2.2 Datasets Analyzed

The number of patients in each datasets will be summarized overall and by treatment strategy group. A listing providing the population membership and the reasons for being excluded from each population will be provided as well.

6.2.3 Demographic and Baseline Characteristics

Demographic data (age at informed consent and gender)as well as baseline characteristics (medical history and atrial fibrillation history) will be summarized using descriptive statistics, overall and by treatment strategy group, for the ITT population.

Demographic and baseline characteristics will be presented overall and by started procedure group (not randomized patients who started the procedure vs. randomized patients), for the started procedure population.

In addition, demographic and medical history for the ITT population will also be presented overall and for the reablated patients (according to CRF reablated form) vs. the non reablated patients.

6.2.4 Compliance

In this study, compliance refers to the patient's compliance in recording and transmitting weekly ECG rhythm strips using the trans-telephonic monitor. For a given patient, compliance will be computed as:

TTM compliance in %: Min [(total # of TTM transmissions / # of weeks in the study) x 100 ; 100]

TTM compliance: Yes if TTM compliance in % ≥ 75%
No if TTM compliance in % < 75%

TTM compliance will be calculated and summarized for the whole study duration, for the period between randomization and Day 90 as well as for the period between Day 91 and study completion. It

will also be calculated by considering only good transmissions and by considering both bad and good transmissions). This will be done for the ITT population.

6.3 Efficacy Analysis

The efficacy analyses will be primarily based on the ITT population but, for illustrative purposes, the primary and some key secondary analyses will be repeated on the evaluable population.

6.3.1 Primary Analysis

The primary analysis will be an unadjusted comparison of time to first recurrence of electrocardiographically documented symptomatic AF/AFL/AT between Day 91 and study completion or any repeat ablation procedure including during the first 90 days between groups. Survival curves will be estimated by the Kaplan-Meier method and the differences between the groups will be assessed using log rank tests. The primary comparison of interest will be between group 1 and group 2. However, to further assess the role of dormant conduction as a predictor of AF recurrence, comparisons between patients without dormant conduction (registry group) to both groups 1 and 2 separately will be examined. The primary analysis will be done on the ITT population and repeated for illustrative purposes on the Evaluable population.

6.3.2 Secondary Analysis

Unless otherwise specified, secondary analysis will be performed on the ITT population.

- Time to first recurrence of electrocardiographically documented symptomatic AF/AFL/AT between Day 91 and study completion OR antiarrhythmic drug use between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days.
- Time to first recurrence of any electrocardiographically documented AF/AFL/AT (symptomatic or asymptomatic) between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days.
- Time to first recurrence of any electrocardiographically documented AF/AFL/AT (symptomatic or asymptomatic) between Day 91 and study completion OR antiarrhythmic drug use between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days.

will be analyzed as the primary endpoint using Kaplan-Meier survival curves and log-rank tests. The analysis of these three key secondary endpoints will be repeated on the Evaluable population.

The proportion of patients experiencing each component of the primary and first three secondary endpoints:

- Symptomatic AF between Day 91 and study completion
- Symptomatic AFL/AT between Day 91 and study completion
- Symptomatic AF/AFL/AT between Day 91 and study completion
- Any AF (symptomatic or asymptomatic) between Day 91 and study completion

- Any AFL/AT (symptomatic or asymptomatic) between Day 91 and study completion
- Any AF/AFL/AT (symptomatic or asymptomatic) between Day 91 and study completion
- Antiarrhythmic drug use between Day 91 and study completion (*secondary endpoint #7*)
- Repeat procedure during the first 90 days

will be displayed as well and compared between the three groups (group 1, group 2 and registry) using chi-square tests on the ITT population. Number of episodes of symptomatic AF/AFL/AT and number of episodes of any AF/AFL/AT (symptomatic or asymptomatic) between Day 91 and study completion will also be provided and compared across groups using a Poisson regression model. Modeling will be done with the SAS GENMOD procedure and the logarithm of the time of follow-up (study completion date – Day 91 + 1) will be used as the offset. It should be noted that the distribution of the number of episodes will be reviewed prior to unblinding and other statistical models may be used if deemed more appropriate.

To analyze the secondary endpoint #8, the proportion of patients experiencing symptomatic AF/AFL/AT and the proportion of patients experiencing any AF/AFL/AT (symptomatic or asymptomatic), with and without antiarrhythmic drug use, will be summarized and compared with chi-square tests across the three groups (group 1, group 2, registry) for the following periods: Day 0 to Day 90 (inclusive), Day 91 to Day 180 (inclusive) and Day 181 to study completion (inclusive). Number of episodes of symptomatic AF/AFL/AT and number of episodes of any AF/AFL/AT (symptomatic or asymptomatic) during these time periods will also be provided and compared, if appropriate, between groups using Poisson regression models.

As additional information on AF/AFL/AT endpoints, the primary endpoint and the secondary endpoint #2 will be derived as described in sections 4.1 and 4.2 but using only the events collected through the AF forms. The same will then be done using only the events collected through the TTM form. Log-rank tests will be used to compare the three groups.

AF burden will be compared across groups using analysis of variance (ANOVA) models. Pairwise comparisons will be done using contrasts under the ANOVA models.

The proportion of patients who will need a repeat ablation procedure will be compared between groups using Chi-Square tests.

The proportion of patients who will visit the emergency room will be assessed at Day 90, Day 180 and Day 365 and will be similarly compared between groups using Chi-Square tests. The same analysis will be done for proportion of patients who will be hospitalized and proportion of patients who will need to be cardioverted.

Occurrence of atrial arrhythmia (Yes/No) between ablation and discharge, between discharge and Day 90, between Day 90 and Day 180 as well as between Day 180 and Day 365 will be presented using counts and proportions, overall and by treatment strategy group. Groups will be compared using Chi Square tests. Related information (number of episodes, symptoms present, per patient's assessment of symptomatic episode(s), etc.) will be summarized using descriptive statistics, overall and by treatment

strategy group. The summary tables will indicate whether the descriptive statistics are based on patients or on episodes. Listings may also be presented as appropriate.

The proportion of patients who will have peri-procedural complications will be compared between the treatment strategy groups using Chi-Square tests. The periods considered will be complications occurring before discharge, from discharge to Day 365 and from Day 0 to Day 365. The proportion of patients with peri-procedural complications will also be presented overall for the non randomized population.

Although not considered as secondary endpoints per se in the protocol, procedure parameters including duration of the procedure, radiofrequency time and fluoroscopy time will be presented overall and by treatment strategy group. These procedure endpoints will be compared between groups ANOVA models. Pairwise comparisons will be done using contrasts under the ANOVA models.

6.3.3 Other Pre Specified Analyses

A series of analyses will be performed after the primary and secondary analyses are completed. They are briefly described in this section and will be conducted on the ITT population, unless otherwise specified.

1. Multivariate Cox model on the primary endpoint

   Dependent variable:
   Time to first recurrence of electrocardiographically documented symptomatic AF/AFL/AT between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days (primary endpoint)

   Covariables :
   - Group (No further ablation vs. Ablation until adenosine)
   - Site
   - Age at consent (date of birth, date of signature of informed consent (CRF p.2)
   - Gender (CRF p.2)
   - Weight (CRF p.6)
   - LA size (CRF p.9)
   - AF duration (CRF p.5)
   - Nb of antiarrhythmic drugs used in the past (CRF p.5)
   - Antiarrhythmic drugs between Day 0 to Day 90 (inclusive)
   - Tobacco (CRF p.4)

2. Multivariate logistic regression model on proportion of patients with AF in the first 90 days

   Dependent variable:

Proportion of patient with electrocardiographically documented symptomatic AF/AFL/AT between Day 0 and Day 90 OR any repeat ablation procedure including during the first 90 days

Covariables :

- Group (No further ablation vs. Ablation until adenosine)
- Site
- Age at consent (date of birth, date of signature of informed consent (CRF p.2)
- Gender (CRF p.2)
- Weight (CRF p.6)
- LA size (CRF p.9)
- AF duration (CRF p.5)
- Nb of antiarrhythmic drugs used in the past (CRF p.5)
- Antiarrhythmic drugs between Day 0 to Day 90 (inclusive)
- Tobacco (CRF p.4)

3. Multivariate recurrent event Cox model on the primary endpoint

Dependent variable:
Time to first recurrence of electrocardiographically documented symptomatic AF/AFL/AT between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days (primary endpoint)

Covariables :

- Group (No further ablation vs. Ablation until adenosine)
- Site
- Age at consent (date of birth, date of signature of informed consent (CRF p.2))
- Gender (CRF p.2)
- Weight (CRF p.6)
- LA size (CRF p.9)
- AF duration (CRF p.5)
- Nb of antiarrhythmic drugs used in the past (CRF p.5)
- Antiarrhythmic drugs between Day 0 to Day 90 (inclusive)
- Tobacco (CRF p.4)

4. Subgroup analyses on the primary endpoint

Dependent variable:
Time to first recurrence of electrocardiographically documented symptomatic AF/AFL/AT between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days (primary endpoint)

Subgroup analyses will be done using a series of Cox models that will include a term for group (No further ablation vs. Ablation until adenosine), a term for the subgroup variable (one at a time) and a group x subgroup interaction term.

Subgroup variables (for continuous variables, median will be used as cutoff point) :

- Age at consent (date of birth, date of signature of informed consent (CRF p.2))
- Gender (CRF p.2)
- Weight (CRF p.6)
- LA size (CRF p.9)
- AF duration (CRF p.5)
- Nb of antiarrhythmic drugs used in the past (CRF p.5)
- Antiarrhythmic drugs between Day 0 to Day 90 (inclusive)
- Tobacco (CRF p.4)

5. Multivariate linear model on ratio of symptomatic AF episodes on any AF episodes

This will be presented for ITT patients who had at least one recurrence of any AF/AFL/AT (symptomatic or asymptomatic) between Day 91 and study completion.

Dependent variable:
Ratio of number of episodes of symptomatic AF/AFL/AT on number of episodes of any AF/AFL/AT (symptomatic or asymptomatic) between Day 91 and study completion.

Covariables :

- Group (No further ablation vs. Ablation until adenosine)
- Site
- Age at consent (date of birth, date of signature of informed consent (CRF p.2)
- Gender (CRF p.2)
- Weight (CRF p.6)
- LA size (CRF p.9)
- AF duration (CRF p.5)
- Nb of antiarrhythmic drugs used in the past (CRF p.5)
- Antiarrhythmic drugs between Day 0 to Day 90 (inclusive)
- Tobacco (CRF p.4)

6. Relationship between patient's assessment of atrial arrhythmia and documented AF

Variables:
Patient's assessment of atrial arrhythmia at any follow-up visit (visit Day 90, visit Day 180 or visit Day 365, CRF p. 26, 32, 37)
Documented episodes AF/AFL/AT

The following 2x2 frequency tables will be provided:

- Atrial arrhythmia (as per patient's assessment) at any visit vs. symptomatic documented AF/AFL/AT between Day 91 and Day 365
- atrial arrhythmia (as per patient's assessment) at any visit vs. documented AF/AFL/AT between Day 91 and Day 365

7. Univariate Cox models on primary and main secondary endpoints

A series of univariate Cox models will be used to identify possible predictors of the primary endpoint and of the three main secondary endpoints:

- Time to first recurrence of electrocardiographically documented symptomatic AF/AFL/AT between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days (primary endpoint)

- Time to first recurrence of electrocardiographically documented symptomatic AF/AFL/AT between Day 91 and study completion OR antiarrhythmic drug use between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days.

- Time to first recurrence of any electrocardiographically documented AF/AFL/AT (symptomatic or asymptomatic) between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days.

- Time to first recurrence of any electrocardiographically documented AF/AFL/AT (symptomatic or asymptomatic) between Day 91 and study completion OR antiarrhythmic drug use between Day 91 and study completion OR any repeat ablation procedure including during the first 90 days.

The following predictors will be investigated. All models will also include the variable group (No further ablation, Ablation until adenosine and Registry).

- Site
- Right Isthmus Linear Ablation (Variable ABL1, CRF p. 21)
- LA Roof Linear Ablation (Variable ABL2, CRF p. 21)
- Left Mitral Isthmus Linear Ablation (Variable ABL3, CRF p. 21)
- Non PV FOCI Ablation (Variable ABL4, CRF p. 21)
- Time of last symptomatic AF/AFL/AT during blanking period (see below)
- Time of last AF/AFL/AT (symptomatic or asymptomatic) during blanking period (see below)
- Presence (yes/no) of at least one symptomatic AF/AFL/AT during blanking period
- Presence (yes/no) of at least one AF/AFL/AT (symptomatic or asymptomatic) during blanking period

- Access to left atrium (CRF p. 14)
- Type of sedation (CRF p. 14)
- Adjunctive mapping systems (CRF p. 14)
- Catheter type (CRF p. 14)
- At least one vein with PV dissociation observed (CRF p. 15)
- At least one vein with PVI performed partially or completely during AF (CRF p. 15)
- At least one vein with spontaneous reconnection (CRF p. 15)

For time of last symptomatic AF/AFL/AT during blanking period, the last symptomatic AF/AFL/AT occurring ≤ Day 90 will be identified and the time (in days) between Day 0 (randomization) and this last event will be computed. This time will then be categorized as follow:

Categories of time last symptomatic AF/AFL/AT during blanking period

Category	Description
None	If no symptomatic AF/AFL/AT occurred between Day 0 and Day 90
Month 1	If at least one symptomatic AF/AFL/AT occurred between Day 0 and Day 90 AND 0 < Time of last symptomatic AF/AFL/AT≤ 30
Month 2	If at least one symptomatic AF/AFL/AT occurred between Day 0 and Day 90 AND 30 < Time of last symptomatic AF/AFL/AT≤ 60
Month 3	If at least one symptomatic AF/AFL/AT occurred between Day 0 and Day 90 AND 60 < Time of last symptomatic AF/AFL/AT≤ 90

Time of last AF/AFL/AT (symptomatic or asymptomatic) during blanking period will be derived similarly.

8. Univariate logistic regression models on dormant conduction

For these models, the unit of analysis will be the vein but the analysis will use generalized estimating equations (GEE) to account for the correlation between veins within patients.

Dependent variable:
Dormant conduction observed (No vs. Transient or Sustained, CRF p. 16))

Covariables :

- Site
- Age at consent (date of birth, date of signature of informed consent (CRF p.2))
- Gender (CRF p.2)
- Weight (CRF p.6)

- LA size (CRF p.9)
- AF duration (CRF p.5)
- Nb of antiarrhythmic drugs used in the past (CRF p.5)
- Use of antiarrhythmic drug at the time of procedure (conmed)
- Tobacco (CRF p.4)
- Access to left atrium (CRF p. 14)
- Type of sedation (CRF p. 14)
- Adjunctive mapping systems (CRF p. 14)
- Catheter type (CRF p. 14)
- At least one vein with PV dissociation observed (CRF p. 15)
- At least one vein with PVI performed partially or completely during AF (CRF p. 15)
- At least one vein with spontaneous reconnection (CRF p. 15)

9. Descriptive statistics for redo

   This will be presented for ITT patients who had a re-ablation (i.e. a Re-Ablation Form is completed in the CRF).

   Information on reconduction status at redo vs. dormant status at initial procedure will be examined by presenting the following 2x2 frequency tables for each group (group 1, group 2 and registry):

   - Variable DCOND (CRF p. 16) vs. PV Reconnection (Variable PVR, CRF Re-Ablation Form) per vein
   - Variable DCOND (CRF p. 16) vs. PV Reconnection (Variable PVR, CRF Re-Ablation Form) all vein combined
   - Variable DCOND (CRF p. 16) vs. PV Isolated (Variable PVI, CRF Re-Ablation Form) per vein
   - Variable DCOND (CRF p. 16) vs. PV Isolated (Variable PVI, CRF Re-Ablation Form) all vein combined
   - Variables S1, SP1, …, I4 (CRF p. 17) vs. variables S1, SP1, …, I4 (CRF Re-Ablation Form, section 2). This analysis will therefore look at redo by vein/segment.

10. Recurrence of AF after second ablation

    This will be presented for ITT patients who had a re-ablation (i.e. a Re-Ablation Form is completed in the CRF).

    Proportion of patients with electrocardiographically documented symptomatic AF/AFL/AT between re-ablation date (as recorded on the Re-Ablation Form) and study completion.

6.4 Procedures, Events and Other Exams Analysis

Unless otherwise stated, procedures, events and other exams analysis will be presented for the ITT population.

6.4.1 Procedure Parameters

Parameters related to the standard pulmonary vein isolation (access to left atrium, type of sedation, esophageal temperature monitoring (Yes/No), etc.) will be summarized using descriptive statistics overall and by treatment strategy group. Listings may also be presented as appropriate.

Additional information captured during the standard pulmonary vein isolation(PV potentials observed (Yes/No), PVI attempted (Yes/No), electrical PVI achieved (Yes/No), etc.) will be summarized for each pulmonary vein using counts and proportions, overall and by treatment strategy group. Similarly, evaluation of dormant conduction post pulmonary vein isolation(dormant conduction observed, dose of adenosine used) will be presented for each pulmonary vein using counts and proportions, overall and by treatment strategy group. Finally, sites where pulmonary vein reconnection will be observed post PVI (SA, S, SP, Posterior, IP, I, IA, Anterior) will be summarized for each pulmonary vein using counts, overall and by treatment strategy group.

In patients randomized to group 2 (Additional ablation until elimination of dormant conduction), information related to the elimination of dormant conduction (dose of adenosine used, number of injections and successful elimination of dormant conduction (Yes/No)) will be presented for each pulmonary vein using counts and proportions. In addition, successful ablation sites for elimination of dormant conduction (SA, S, SP, Posterior, IP, I, IA, Anterior) will be summarized for each pulmonary vein using counts.

Information on other ablation (right isthmus linear ablation (Yes/No), LA Roof linear ablation (Yes/No), etc.) will be presented using counts and proportions, overall and by treatment strategy group.

Most tables in this section will present information broken down by pulmonary vein. To get a more global picture, information related to the right veins (RSPV, RIPV, RCPV and RMPV), the left veins (LSPV, LIPV, LCPV and LMVP) and all the veins, will be combined and summarized as defined above. However, in the corresponding tables, counts will refer to number of veins instead of number of patients.

6.4.2 Concomitant Medications

Concomitant medications will be collected throughout the study, starting at baseline (study entry) and will be coded with respect to indication and generic name using the WHO drug dictionary (version Sep 2012). Frequency of use of concomitant medications will be presented for the subjects of the ITT population by both indication and generic name, overall and by treatment strategy group.

A listing of concomitant medications will also be provided.

6.4.3 Adverse Events and Serious Adverse Events

AEs recorded in the CRF will be coded by system organ class and body system according to the MedDRA dictionary (version 15.1). AEs and SAEs recorded in the CRF will be listed. A listing will also be generated for SAEs adjudicated by the adjudication committee.

6.4.4 Trans-Telephonic Monitor

Proportion of patients who received a TTM at discharge and proportion of patients who transmitted a trans-telephonic recording at Day 90, Day 180 and Day 365 will be presented for group 1 and group 2, as well as for the registry group.

6.4.5 Other Exam Analysis

Parameters related to the various exams will be summarized using descriptive statistics. For assessments done at baseline, before the ablation and at discharge, descriptive statistics will be presented overall and by treatment strategy group. For assessments done at Day 90, Day 180 and Day 365, descriptive statistics will be presented similarly, but without the usual medical care group. Listings may also be presented as appropriate.

6.4.6 Laboratory parameters

Laboratory parameters (potassium, hemoglobin, platelets, etc.) measured before the ablation will be summarized using descriptive statistics overall and by treatment strategy group.

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2 Efficacy analysis

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