Guidance for Industry and FDA Staff

Clinical Study Designs for Catheter Ablation Devices for Treatment of Atrial Flutter

Document issued on: August 5, 2008

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Food and Drug Administration
Center for Devices and Radiological Health

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Office of Device Evaluation

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Preface

Public Comment

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Table of Contents

1. INTRODUCTION 1

The Least Burdensome Approach 1

2. BACKGROUND 2

3. SCOPE 3

4. STUDY DESIGN 4

A. Randomized Controlled Trials (RCTs) 4

B. Alternatives to RCTs 5

C. General Design Considerations 6

5. STUDY ENDPOINTS 7

A. Primary Effectiveness Endpoint - Rhythm 7

B. Safety Endpoint – Ablation Device/Procedure 7

6. STUDY GROUPS 8

7. STATISTICAL CONSIDERATIONS 9

8. SAMPLE SIZE 10

9. FOLLOW UP OF STUDY SUBJECTS 10

10. ANTICOAGULATION PARAMETERS 10

11. INVESTIGATOR SELECTION AND TRAINING 11

12. DATA COLLECTION FORMS 11

13. STUDY MONITORING 11

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This guidance addresses the use of a randomized clinical trial (RCT) approach in designing clinical studies for catheter ablation devices for the treatment of atrial flutter. The first several premarket approval (PMA) applications approved for the treatment of atrial flutter relied on clinical data from single-arm trials because no devices were approved for treatment of atrial flutter. Recently approved IDE studies and PMA applications have used the option of a RCT given the availability of PMA-approved ablation catheters indicated for treatment of atrial flutter. This guidance provides recommendations about the clinical study designs that rely on a RCT.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe should be addressed before your device can be marketed. In developing the guidance, we carefully

considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

2. Background

Atrial flutter (AFL) is a rapid regular atrial contraction occurring usually at rates between 250 and 350 beats per minute and thought to be a relatively common arrhythmia . However, the epidemiology of atrial flutter has not been studied as thoroughly as that of atrial fibrillation (AF). In one epidemiologic study, the overall incidence of atrial flutter was 0.088% (or 88 per 100,000 people).[1] Over one-half of these patients also had atrial fibrillation. Atrial flutter alone was seen in 0.037% of the study population. The incidence of atrial flutter increased markedly with age, from 5 per 100,000 of those older than 50 years of age to 587 per 100,000 for those older than 80 years of age. Atrial flutter was more than twice as common in men compared to women. The incidence of atrial flutter has been reported to be approximately twice that of paroxysmal supraventricular tachycardia.[2]

Endocardial mapping suggests that typical atrial flutter is based on right atrial macro reentry which involves the isthmus between the inferior vena cava (IVC) and the tricuspid annulus (TA). The most common form demonstrates a counterclockwise circuit around the tricuspid

[1] Granada J, et al. Incidence and predictors of atrial flutter in the general population. Journal of the American College of Cardiology. 2000; 36: 2242-2246.

[2] Orejarena L, et al. Paroxysmal Supraventricular Tachycardia in the General Population. Journal of the American College of Cardiology. 1998; 31: 150-157.

valve.[3] Current treatments span a spectrum of non-invasive to invasive options and include pharmaceutical, catheter-based, and other device-based approaches. Literature reports of early success with catheter ablation[4] (initially 4 or 5 mm tip manually deflectable catheters using radiofrequency energy and fluoroscopic guidance) have led to the development of non-traditional ablation catheters and ablation systems (large tip catheters,[5] electroanatomic mapping systems[6,7], remote navigation systems, and alternate energy sources[8]).

Since 2003, FDA has approved premarket approval (PMA) applications for ablation catheter systems indicated for the treatment of atrial flutter. The first several PMAs relied upon clinical data from single-arm trials because no devices were approved for treatment of atrial flutter at that time. Subsequently, recently approved IDE studies and PMA applications have reflected a randomized clinical trial (RCT) approach given the availability of PMA-approved ablation catheters indicated for treatment of atrial flutter.

3. Scope

For the purpose of this guidance document, FDA defines type I atrial flutter as a cavotricuspid dependent, right atrial macro-reentrant arrhythmia.

The product code for this category of device is:

OAD - Cardiac ablation percutaneous catheter, intended for treatment of atrial flutter

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[3] Saoudi N, et al. A classification of atrial flutter and regular atrial tachycardia according to electrophysiological mechanisms and anatomical bases. European Heart Journal. 2001; 22: 1162-1182.

[4] Cauchemez B, Haissaguerre M, et al. Electrophysiological Effects of Catheter Ablation of Inferior Vena Cava–Tricuspid Annulus Isthmus in Common Atrial Flutter. Circulation. 1996; 93: 284-294.

[5] Scavee C, Haissaguerre M, et al. Prospective randomised comparison of irrigated-tip and large-tip catheter ablation of cavotricuspid isthmus-dependent atrial flutter. European Heart Journal. 2004; 25; 963–969.

[6] Kottkamp H, et al. Electromagnetic Versus Fluoroscopic Mapping of the Inferior Isthmus for Ablation of Typical Atrial Flutter. Circulation. 2000; 102: 2082-2086.

[7] Willems S, et al. Catheter ablation of atrial flutter guided by electroanatomic mapping (CARTO): a randomized comparison to the conventional approach. Journal of Cardiovascular Electrophysiology. 2000; 11: 1223–1230.

[8] Timmermans C, et al. Randomized Study Comparing Radiofrequency Ablation With Cryoablation for the Treatment of Atrial Flutter With Emphasis on Pain Perception. Circulation. 2003; 107: 1250-1252.

These devices are class III, requiring PMA approval before marketing (section 513(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360c(a)).

Devices excluded from the scope of this guidance include:

- electrode recording catheters or probes (product code DRF, 870.1220),
- cardiac ablation percutaneous catheters (product code LPB), and
- percutaneous catheters intended for treatment of atrial fibrillation (product code OAE).

FDA believes that the devices addressed by this guidance document are significant risk devices as defined in 21 CFR 812.3(m).[9] In addition to the requirement of having an FDA-approved IDE (21 CFR Part 812), sponsors of such studies must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).[10]

4. Study Design

FDA recognizes that there is no unique "best design" for clinical investigations of devices. The elements discussed in this document embody FDA's current thinking regarding appropriate study designs for these devices. The design, execution, and analysis of any clinical trial of a device should be capable of developing data that demonstrates the safety and effectiveness of the device for its intended use and patient population.

A. Randomized Controlled Trials (RCTs)

In general, RCTs provide the least burdensome means of providing reasonable assurance of the safety and effectiveness of devices for catheter-based ablation of atrial flutter. It

[9] Please refer to Blue Book Memorandum entitled "Significant Risk and Nonsignificant Risk Medical Device Studies," http://www.fda.gov/cdrh/d861.html.

[10] You should review the statutory definition of applicable clinical trial to determine whether your trial must be registered to comply with the law. *See* PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)). http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf Information can be submitted to ClinicalTrials.gov using the Protocol Registration System (PRS). For more information visit the PRS Information Page (http://prsinfo.clinicaltrials.gov).

generally is feasible to conduct RCTs for atrial flutter ablation devices.[11,12,13] Potential advantages to RCT designs include an improved ability to compare effectiveness of the investigational device to devices approved for treatment of atrial flutter. Different patient demographics (e.g., a patient with co-morbid conditions versus a patient with only atrial flutter) may have different inherent safety and effectiveness profiles. As a result, it may be challenging for a performance-goal study design to account for any differences in patient demographics, which may be difficult to control. Assurance that subject populations are similar in test and control groups is best attained by randomly dividing a single sample population into groups that receive the test or control treatments. Randomization avoids systematic differences between groups with respect to known or unknown baseline variables that could affect outcome. Inability to eliminate systematic differences between treatment groups is a major problem of studies without a concurrent randomized control. Randomization also provides a sound basis for statistical inference.

Potential advantages to RCT designs extend not only to evaluation of device effectiveness but also to evaluation of device safety. Adverse event rates may be affected by factors such as patient characteristics, concomitant cardiopulmonary disease, device design, evolving procedural methods and operator experience and may be difficult to evaluate using data from an historical control.

B. Alternatives to RCTs

Although FDA recommends RCTs, we will consider alternative study designs if they are scientifically sound and address the relevant questions. Regardless of the study design that is used, the data to support PMA approval should be of sufficiently high quality to adequately demonstrate that an acceptable risk-benefit profile exists and that the device provides a reasonable assurance of safety and effectiveness. In practice, this means that the burden of proof may be concurrently greater as the study design departs further from the RCT design (e.g., missing data may be less tolerable in a single-arm design). Alternative study designs may include, but are not limited to, reliance on valid non-U.S. data where appropriate for the

[11] Kasai A, et al. Comparison of Effectiveness of an 8-mm Versus a 4-mm Tip Electrode Catheter for Radiofrequency Ablation of Typical Atrial Flutter. American Journal of Cardiology. 2000; 86: 1029-1032.

[12] Schreieck J, et al. Prospective Randomized Comparison of Closed Cooled-tip Versus 8-mm-Tip Catheters for Radiofrequency Ablation of Typical Atrial Flutter. Journal of Cardiovascular Electrophysiology. 2002: 13: 980-985.

[13] Fuster V, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation. Journal of the American College of Cardiology. 2006;48:e149-246.

intended U.S. patient population (21 CFR 814.15), study designs employing matched controls for safety evaluation, and performance goals for safety and/or effectiveness.

There may be other valid study designs that are not discussed in depth in this guidance. For example, an alternate design could include a concurrent, non-randomized control comparing a new device to an approved device. In such a design, it is important to match the subject's characteristics of the investigational treatment arm and the concurrent control arm. Another alternate study design could include a single arm trial using established performance goals. In this study design, FDA would evaluate the safety and effectiveness strictly based on the pre-specified performance goals. If you propose an alternative study design, we recommend that you explain thoroughly the scientific arguments supporting your design. For example, if you elect to use a performance goal approach, the specific literature and rationale justifying this approach should be explained in detail. You should also be aware that FDA's evaluation of the claims allowed in labeling will likely be guided, in part, by the design and results of the associated clinical trial.

C. General Design Considerations

The objective of ablation treatment for atrial flutter is to reduce or eliminate long-term recurrence of atrial flutter. We recommend that chronic success (defined as the absence of recurrent atrial flutter at 6 months post-ablation) should be the primary effectiveness endpoint. However, under certain conditions, FDA believes there is sufficient scientific evidence to indicate that acute procedural success (defined as the creation of bidirectional block at the cavo-tricuspid isthmus) is predictive of chronic success. We believe acute procedural success may be appropriate to serve as a surrogate effectiveness endpoint for catheters provided all of the following device characteristics are present:

- creates endocardial lesions
- manipulated in the endovascular space
- a single ablation electrode
- the energy source is radiofrequency (RF)
- temperature sensing capability
- "steerable" (i.e., catheter has a tip which is manually-deflectable via a thumb-wheel or similar mechanism residing on the handle of the catheter)
- percutaneous placement.

At this time, we believe the surrogate effectiveness endpoint may not be appropriate for catheters with alternate energy sources, and novel approaches to navigation and/or steering.

5. Study Endpoints

A. Primary Effectiveness Endpoint - Rhythm

As described above, the primary effectiveness endpoint for catheter ablation devices intended for the treatment of atrial flutter should be chronic success, which is defined as the absence of recurrent atrial flutter at 6 months post-ablation. For select catheters described in the preceding section where sufficient clinical evidence has validated acute procedural success as a surrogate for the chronic endpoint, a surrogate endpoint may be appropriate. Acute procedural success should be defined as the creation of bidirectional conduction block across the cavo-tricuspid isthmus.[4,7,14] Ideally, this assessment should be done in the absence of anti-arrhythmic drugs. If an anti-arrhythmic drug is used in the follow-up period to treat atrial flutter, we recommend that the subject be counted as a chronic treatment failure. If an anti-arrhythmic drug is used to treat an arrhythmia other than atrial flutter, and there is no evidence of atrial flutter recurrence, the subject may be considered to be a chronic treatment success.

The preferred modality for assessing effectiveness is a periodic review of the subjects' symptoms, along with surveillance rhythm monitoring (Holter monitoring, resting ECG recording and/or event monitoring can be considered).

B. Safety Endpoint – Ablation Device/Procedure

FDA recommends the safety endpoint be a composite serious adverse event endpoint and, at a minimum, include the following:

- cardiac perforation/tamponade
- cerebrovascular accident
- complete heart block
- death
- myocardial infarction
- pulmonary embolism

[14] Poty H, Saoudi N, et al. Radiofrequency Catheter Ablation of Atrial Flutter: Further Insights Into the Various Types of Isthmus Block: Application to Ablation During Sinus Rhythm. Circulation. 1996; 94: 3204-3213.

- transient ischemic attack
- additional risks specific to the device that need to be measured.

We recommend you collect relevant major complication information for 7 days after the ablation is performed. We believe this 7-day period provides an accurate assessment of the types and frequencies of safety problems that can occur after ablation and is consistent with how safety is assessed for other types of cardiac ablation devices. FDA recommends that you include an independent clinical events committee to evaluate adverse events. (21 CFR 812.25(b))

6. Study Groups

You should clearly define your study inclusion and exclusion criteria. Examples of appropriate inclusion and exclusion criteria for catheter ablation studies designed to treat atrial flutter are listed below.

Suggested Inclusion Criterion

- Subjects with at least one documented episode of Type I atrial flutter in the six month period preceding the date of enrollment in the study and are clinically indicated for catheter ablation.

Suggested Exclusion Criteria

- Any prior right atrial cavo-tricuspid isthmus ablation
- Subjects who cannot have anti-arrhythmic drugs stopped for at least 5 half-lives prior to the procedure (for class I and class III anti-arrhythmic drugs) or for at least 4-6 months for amiodarone
- Myocardial infarction within the prior two months
- Current unstable angina
- Cardiac surgery within the prior three months
- Currently documented intracardiac thrombus by transesophageal echocardiography
- Permanent leads in or through the right atrium
- Clinically significant tricuspid valve regurgitation or stenosis
- Uncompensated congestive heart failure
- Any cerebral ischemic event (including transient ischemic attacks) in the prior six months

- Clinically significant coagulation disorder
- Pregnancy
- Uncontrolled hyperthyroidism
- Current enrollment in any other clinical investigation
- Any other significant uncontrolled or unstable medical condition
- Life expectancy of less than two years.

Exclusion criteria should be designed to minimize the risk of underlying medical conditions from having a substantial impact on the evaluation of the safety profile of the device. Specific criteria may not be applicable to all devices. In addition, FDA will evaluate scientifically valid justifications for why specific subject populations cited above should not be excluded.

7. Statistical Considerations

The study design should be clearly described in the protocol. For example, the treatment allocation ratio to the treatment arms, the randomization scheme, and the implementation of blinding/masking, if any, should be clearly described for a randomized design. Safety and effectiveness endpoints and their hypotheses both in words and mathematical forms should be clearly stated.

Pre-specification of the statistical analysis is a key factor for obtaining consistent and convincing evidence of device safety and effectiveness. Therefore, we recommend that you pre-specify:

- the hypothesis tests used to evaluate the safety and effectiveness endpoints
- plans for checking any assumptions required for the validity of these tests
- alternative procedures/tests to be used if the required assumptions are not met
- a clear study success criterion that indicates which hypotheses must be met in order for the study to be considered a success.

The study protocol should clearly define the study population to be analyzed (e.g., intent-to-treat or per-protocol). If secondary endpoints and hypotheses for which labeling claims (such as presentation of p-values or confidence intervals) are intended, your protocol should pre-specify an appropriate testing procedure that for preservation of Type I error in the setting of multiple comparisons.

In addition, FDA recommends that the investigational protocol pre-specify one or more methods for handling missing data during data anaylsis.

8. Sample Size

We recommend that you provide a relevant statistical justification for any sample size calculation. FDA recommends that sponsors perform both safety endpoint and effectiveness endpoint calculations appropriate for the hypotheses and tests specified on these endpoints. Generally, the larger sample size should be the one employed in the study.

9. Follow Up of Study Subjects

We recommend that you develop standardized monitoring protocols and include, at a minimum, a telephone call at 7 days and outpatient follow up visits at thirty days and six months. If acute procedural success is used as a surrogate primary effectiveness endpoint for qualified devices, the duration of the study (and thus the final follow-up visit) may be less than 6 months. These visits should typically include documentation of symptoms and assessment of cardiac rhythm with a 12 lead electrocardiogram (ECG), or other equivalent cardiac rhythm measurement. When symptoms suggestive of recurrent atrial flutter occur, rhythm documentation with transtelephonic event monitoring is recommended.

The importance of adequate and appropriate follow-up of study subjects cannot be overemphasized. Our experience is that many clinical investigators omit or perform incomplete post-procedure testing and evaluations once the procedure has been completed. Results obtained from effective follow-up contribute significantly to the demonstration of safety and effectiveness; therefore, the study protocol should be strictly followed without omission of post-procedure testing.

10. Anticoagulation Parameters

Current guidelines[15,16] recommend that the guidelines for atrial fibrillation be extended to atrial flutter. If a subject is likely to be in atrial flutter at the time of the ablation (and

[15] Fuster V, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation. Journal of the American College of Cardiology. 2006;48:e149-246.

[16] Blomström-Lundqvist Carina, et al. ACC/AHA/ESC Guidelines for the Management of Patients With Supraventricular Arrhythmias*—Executive Summary. Circulation. 2003;108(15):1871-1909.

therefore is to undergo termination of the atrial flutter), FDA recommends that he or she receive 3 to 4 weeks of therapeutic anticoagulation prior to the ablation. A reasonable alternative could include a pre-procedural trans-esophageal echocardiogram which reveals no evidence of left atrial appendage thrombus. Subjects in atrial flutter at the time of the procedure should receive at least 3 to 4 weeks of post-procedural therapeutic anti-coagulation. FDA will entertain alternative approaches based on their scientific and clinical merit.

11. Investigator Selection and Training

FDA recommends that you base your selection of investigators on their scientific training and clinical experience, i.e., physicians trained in catheter ablation and board-certified in electrophysiology. However, in situations in which the investigator lacks a thorough knowledge of study procedures, you should train the investigator prior to study initiation. In addition, the selection of a study site with site staff trained in study procedures to assist the investigator with appropriate data collection and subject follow-up is an important factor in determining whether the site is fully qualified to conduct the study.

12. Data Collection Forms

FDA recommends that you design the case report forms to optimize collection of information relevant to the primary safety and efficacy endpoints, minimizing the accumulation of data that may be peripheral or irrelevant to the clinical study. Experience has shown that this approach can reduce the total number of data point errors and thereby diminish the amount of time and effort needed for the data clean-up process.

13. Study Monitoring

In designing your studies with atrial flutter ablation devices, we feel it is essential that you develop a comprehensive monitoring plan for these studies. Sponsors are required to include written monitoring procedures in applications for investigational device exemptions (21 CFR 812.25(e)). Experience has shown that when sponsors make adequate provisions for monitoring studies, and assuring prompt corrections to departures from the investigational plan, the quality of the resulting submission is improved. Therefore, we recommend selecting qualified monitors, adherence to the investigational plan and other requirements, and investigators' compliance with record-keeping and reporting obligations.

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