REVELATION® Tx Microcatheter Ablation System (P020039)
Cardima, Inc.

CLINICAL STUDY SUMMARY

TABLE OF CONTENTS

1.0 BACKGROUND 1
- **1.1 Public Health Need 1**
- **1.2 Natural History of Paroxysmal Atrial Fibrillation 1**
- **1.3 Current Standards of Care and the Unmet Patient Needs 1**
  - **1.3.1** Pharmacologic Therapy 1
  - **1.3.2** Cox-Maze Surgical Procedure 2
  - **1.3.3** Catheter Ablation 2
- **1.4 Device Design Rationale 3**
- **1.5 Device Description 3**
- **1.6 Proposed Indications for Use 4**
- **1.7 History of Clinical Study Design 4**

2.0 BIOCOMPATIBILITY AND ELECTROMECHANICAL STUDIES 5
- **2.1 Biocompatibility Studies 5**
- **2.2 Electromechanical Studies 8**
  - **2.2.1** Electrical Performance Testing 8
  - **2.2.2** Mechanical Performance Testing 8
  - **2.2.3** Radiopacity Testing 9

3.0 ANIMAL STUDIES 10

4.0 PHASE IIA FEASIBILITY STUDY 12

5.0 PHASE IIB CLINICAL STUDY 12
- **5.1 Study Design 12**
- **5.2 Study Results 12**

6.0 CLINICAL STUDY DESIGN 13
- **6.1 Summary 13**
- **6.2 Objectives 13**
- **6.3 Endpoints and Rationale 14**
- **6.4 Subject Population 14**
  - **6.4.1** Inclusion Criteria 15
  - **6.4.2** Exclusion Criteria 15
  - **6.4.3** Recruitment 15
- **6.5 Follow-up Assessment 16**
- **6.6 Pre-Enrollment Baseline Testing 17**
- **6.7 Study Procedure 17**
- **6.8 Adverse Events 18**
- **6.9 Statistical Methods 18**

6.10 Methods to Reduce Study Bias 19

7.0 CLINICAL STUDY RESULTS 20
7.1 Study Sites 20
7.2 Subject Enrollment by Site 20
7.3 Baseline Characteristics 21
7.3.1 Demographic Characteristics 22
7.3.2 Medical Characteristics – Cardiovascular Disease 22
7.3.3 EKG Findings at Baseline 23
7.3.4 Medical Characteristics – Other Disease 24
7.3.5 Baseline Cardiac Status 25
7.3.6 Baseline Quality of Life 27
7.3.7 Medications at Baseline 28
7.4 Subject Flow Chart 29
7.5 Procedural Results 31
7.5.1 Posterolateral and Septal Lesions 31
7.5.2 Isthmus Lesion 32
7.6 Endpoints 33
7.6.1 Primary Endpoints 33
7.6.2 Secondary Endpoint 39
7.7 Additional Results 42
7.7.1 Symptoms Associated with AF Episodes 42
7.7.2 EKG Findings in Follow-up 43
7.7.3 NYHA Status 44
7.7.4 Hospitalizations and Emergency Room Visits 45

8.0 RISK/BENEFIT ANALYSIS 46
8.1 Benefits 46
8.2 Risks 47

9.0 CONCLUSIONS 49

REFERENCES

1.0 BACKGROUND

1.1 Public Health Need

Atrial fibrillation (AF) is a complicated cardiac arrhythmia that has become increasingly important as the number of elderly individuals within the population grows. Overall, it is estimated that at least 2.2 million Americans have paroxysmal or persistent AF.[1] AF is the most common rhythm disorder among United States (US) patients hospitalized with a primary diagnosis of arrhythmia.[2] From 20 years ago, there has been a 66% increase in hospital admissions due to AF, and it can only be presumed that this number will continue to grow with the aging population.[3] AF has an estimated prevalence of 0.4% to 1.0% in the general population, increasing with age (the median age for AF patients is about 75 years old).[4] There is a strong likelihood that the prevalence of AF may be substantially underestimated due to underdetection and undersampling in patients with paroxysmal AF.[5]

AF is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality, especially in women.[6] Atrial fibrillation is an independent risk factor for stroke that is associated with a four to five-fold higher risk than in the non-AF population.[7] In regards to paroxysmal AF, patients are often highly symptomatic. Van den Berg documented significant impacts of paroxysmal AF on the Medical Outcomes Study's Short-form 36 (SF-36) scores, especially in the areas of physical role function, emotional role function, vitality and general health.[8] Individuals with AF are usually symptomatic; 85% of patients report palpitations, dyspnea, fatigue, and chest pain.[9]

1.2 Natural History of Paroxysmal Atrial Fibrillation

The pathophysiologic mechanisms underlying paroxysmal AF are beginning to be elucidated but are still not fully known. Generally AF is thought to result from: 1) AF triggers, 2) transitional tachycardias, and 3) maintenance resulting from re-entrant circuits in distinct atrial regions.[10] Jais provided evidence that at least a subset of drug-refractory paroxysmal AF is explained by arrhythmogenic foci in the atria.[11] It has been shown that paroxysmal AF will progress into chronic atrial fibrillation if left untreated.[12]

1.3 Current Standards of Care and the Unmet Patient Needs

1.3.1 Pharmacologic Therapy

Treatment of paroxysmal atrial fibrillation (PAF) focuses on restoring and maintaining a normal sinus rhythm, and preventing the occurrence of a stroke. Standard treatment for paroxysmal AF is pharmacotherapy, consisting of antiarrhythmic drugs (AADs) used to keep patients in normal sinus rhythm although many of the drugs are limited in their use because of challenging side-effect profiles,

and the fact that over time, patients commonly become refractory to the treatment. Administration of flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacological cardioversion of AF.[13] Sotalol can be beneficial in outpatients in sinus rhythm with little or no heart disease who are prone to paroxysmal AF, but there is not a strong body of evidence to support this recommendation.[13] Evidence suggests that amiodarone is more effective than other drugs to maintain sinus rhythm in patients who are symptomatic or who have become refractory to other drugs. However, it is associated with a relatively high incidence of potentially severe extracardiac toxic effects.[13]

In stable patients, control of the heart rate often provides relief of symptoms. However, some patients remain symptomatic despite a controlled heart rate and experience side-effects from pharmacologic therapy. Bradycardia and heart block may occur as an unwanted effect of beta blockers, amiodarone, digitalis glycosides, or calcium channel antagonists, particularly in patients with paroxysmal AF, and the elderly.[13]

1.3.2 Cox-Maze Surgical Procedure

The surgical approach to AF treatment is typically reserved for people with AF associated with structural heart disease (e.g., rheumatic or congenital heart disease). The "Maze" procedure, developed by Cox, involves incision and repair of the atria at any of several locations; it is usually performed simultaneously with valve replacement or other cardiac surgery. Complete elimination of AF episodes and symptoms has been demonstrated in over 90% of patients undergoing this surgical procedure.[14] Although the Cox-Maze procedure is widely recognized as the gold-standard treatment for atrial fibrillation due to its high success rate and long-term effectiveness, it is rarely performed in patients not having an indication for cardiac surgery; thus, widespread treatment of AF via this option is limited.

1.3.3 Catheter Ablation

In the 2006 guidelines published by the American Heart Association, American College of Cardiology and the European Society of Cardiology,[13] catheter ablation received recognition for its increased role, concordant with a growing body of evidence, for treatment of AF. Left sided approaches to ablating the pulmonary veins have received a great deal of attention in the electrophysiology community in the past 10 years. The literature has reported cure rates with left sided approaches to be relatively high, but it must be noted that re-ablation is very often necessary. Additionally, the left-atrial approach is substantially marred by its complexity and the frequency of severe adverse effects such as stroke and pulmonary vein stenosis.[15,16,17]

Published or spoken success rates for left atrial ablation are hard to quantify because of differing procedures and catheter systems, and because most are single-center and

often single investigator studies. Left-sided ablation procedures are often quoted as having good success rates, but these results are typically reported from single centers with a single investigator, and often only after a second ablation procedure. The results of a recent study from researchers at the Johns Hopkins University School of Medicine help instill some realism about the general success rates in current clinical practice. The investigators reported the 2-year success rates (defined as freedom from symptomatic AF on and off of drug therapy) after a single left-sided ablation procedure in 200 consecutive patients treated at their center as being 28% in patients who underwent a single procedure and 41% when incorporating the outcomes of those patients who underwent a repeat procedure.[18]

1.4 Device Design Rationale

The rationale for right atrium ablation is based on the success of the Cox-Maze procedure, the variable pathophysiology of AF across patients, and the results of bi-atrial mapping studies indicating the origin of premature beats from the right atrium.[19,20,21] At the Boston Atrial Fibrillation Conference in 2007, the importance of right-atrium ablation was re-emphasized, in light of the now known unreliability of left-sided procedures.

Cardima developed the REVELATION® Tx Microcatheter Ablation System, to create precise linear or ablation scars that mimic those made during the maze surgery, but from an endovascular approach and using radiofrequency energy. Linear ablations have an advantage over conventional "drag and burn" techniques; there is less risk for fistula or damage to the heart tissue; and it is procedurally less-complicated for the physician to produce physiologically complete transsection of electrical pathways. Furthermore, potential advantages of the REVELATION® Tx Microcatheter Ablation System include:

1. Placement of the catheter into the right atrium via the femoral vein is straightforward.

2. Positioning of lesions in the right atrium requires a minimum of manipulation of the catheter.

3. The instructions for use for the catheter are easily understood.

4. As shown in animal studies and with electroanatomic imaging, the lesions produced by the REVELATION® Tx Microcatheter in the right atrium are continuous and block electrical signals through the heart.

1.5 Device Description

This REVELATION® Tx Microcatheter Ablation System consist of a single use, steerable, multi-electrode ablation microcatheter (3.7F) with an atraumatic, flexible, non-electrically active tip, and a single-use deflectable NAVABLATOR® "single tip"

ablation catheter (8F) with an electrically active tip. Accessories to the REVELATION® Tx Ablation System include Cardima's guiding catheter, NAVIPORT (K974683), the Tx SELECT™ Switchbox and associated connecting cables. The connecting cables and the passive switchbox are the interface between both ablation catheters and any commercially available electrocardiograph, pacing stimulator and any commercially available endocardial radiofrequency (RF) generator that is thermocouple-compatible.

The REVELATION® Tx Microcatheter has eight flexible electrodes and eight thermocouple temperature sensors in a linear array on the distal end of the catheter. The most distal tip of the catheter is a highly flexible (floppy), non-electrically active platinum coil for fluoroscopic visualization and atraumatic placement. The REVELATION® Tx is designed for the creation of thin linear lesions in the atrium for the treatment of atrial fibrillation by placing the linear array of electrodes along a desired trajectory in the atrium, conforming to the curvature of the wall.

The companion endocardial ablation catheter, NAVABLATOR®, has four electrodes, one of which is the "hot tip" RF ablation electrode with a thermocouple embedded in its tip. The NAVABLATOR® is intended for the creation of lesions (either linear or focal) from its tip when diverse myocardial anatomy requires the features of a "hot tip" ablation catheter to achieve effective lesions.

Both ablation catheters in this system are designed for mapping intracardiac potentials, pacing and ablating cardiac tissue with RF energy.

1.6 Proposed Indications for Use

The REVELATION® Tx Microcatheter Ablation System is indicated for the symptomatic treatment of drug-refractory paroxysmal atrial fibrillation by creating continuous RF ablation lesions in the right atrium.[a]

1.7 History of Clinical Study Design

The study was designed in accordance with the recommendations of an FDA Circulatory System Devices Panel Meeting (July 22, 1998). The Panel recommended a single-arm, non-randomized trial design with subjects as their own control. It also recommended that the subject population consist of individuals who failed two anti-arrhythmic drugs or amiodarone. The baseline AF count was suggested to be two episodes over three months, and subjects should be followed for six months post-

[a] This revised indication for use was submitted to ODE on December 28, 2005 in PMA amendment 011. Cardima believes that the data provided in the PMA fit the revised indication better than the original indications for use statement, which was the subject of the supervisory review. That indication was: "for the treatment of atrial fibrillation (AF) in patients with drug-refractory paroxysmal atrial fibrillation by mapping, pacing and ablating with a compatible radiofrequency generator, creating a set of continuous linear lesions along the lateral and septal walls and along the isthmus of the right atrium."

ablation. The Panel recommended that success be considered a 50 – 75% reduction in the frequency of symptomatic AF episodes. Specifically, the Panel noted that improved quality of life may be a "very important outcome." The Cardima trial contained all of these elements, with the exception that subjects had to have three episodes of AF or more to qualify for the trial.

2.0 BIOCOMPATIBILITY AND ELECTROMECHANICAL STUDIES

2.1 Biocompatibility Studies

The REVELATION® family of catheters originated as mapping and pacing catheters and evolved to include products that also had the capability of delivering RF energy for ablation. The evolution of these products included some dimensional changes and some electronic changes, such as the addition of thermocouples, but the product materials and manufacturing process changed only minimally. In addition, the REVELATION® family of products experienced a number of name changes (**Table 1**).

TABLE 1
REVELATION®/Pathfinder Product Name History

Original Name	Regulatory Approval	Second Name	Current Name
Pathfinder 1.8mm, 2.5F	K955802 (01/29/97)	Pathfinder	Pathfinder
Pathfinder 3mm, 3.3F	K970853 (11/04/97)	Pathfinder AF	REVELATION AF
Pathfinder 1mm, 1.5F	K971975 (07/01/97)	N/A	Pathfinder Mini
Pathfinder AFTC	Pending	Pathfinder AFTC	REVELATION® Tx

The Cardima REVELATION® product family is categorized as an external communicating device that is in contact with circulating blood for less than 24 hours (Level 1). No blood-contacting colorants are used in the manufacture of these devices.

Biocompatibility testing was performed consistent with ISO 10993, "Biological Evaluation of Medical Devices" requirements for this type of blood contact. Finished, sterilized product was used for this GLP testing. The device under test was the Pathfinder 2.5F (K955802). The test results demonstrated that the biocompatibility of the Pathfinder 2.5F was acceptable for its classification of blood contacting devices. **Table 2** summarizes the biocompatibility testing that was completed and the test results.

The Pathfinder 2.5F is a mapping catheter that, with the exception of thermocouples, comprises the same components and materials as the REVELATION® Tx Microcatheter and is subject to the same manufacturing process. Because the thermocouples have no blood contact, separate biocompatibility testing of the REVELATION® Tx Microcatheter would not reveal any new biocompatibility information. The test results for the Pathfinder 2.5F adequately represent the biocompatibility of the REVELATION® Tx Microcatheter.

TABLE 2
Biocompatibility Test Summary

Test	Summary of Results	Conclusion
In-Vitro Cytotoxicity	No evidence of causing cell lysis or toxicity greater than mild reactivity	Acceptable
In-Vitro Hemolysis	Mean hemolysis = 0%, 1%	Acceptable
USP Acute Systemic Toxicity in Mice	Treated mice did not exhibit significantly great reaction than control mice	Acceptable
USP Intracutaneous Toxicity in Rabbit (Acute)	No evidence of significant irritation or toxicity	Acceptable
Delayed Contact Sensitization in the Guinea Pig (Maximization Method)	No evidence of causing delayed dermal contact sensitization	Acceptable
Thromboresistance in Dog	Minimal to no thrombus formation	Acceptable
Rabbit Pyrogen Study	Judged as non-pyrogenic	Acceptable
C3a Complement Activation	Lower than "Low biomaterial reference control" *No longer required due to ambiguity of results*	Acceptable
USP Muscle Implantation in Rabbits	Macroscopic reaction not significant; microscopically, a slight irritant *(Not required for external communicating blood contacting devices [<24 hour contact])*	Acceptable
Subchronic Intravenous Toxicity in Mice	No significant evidence of toxicity *(Not required for external communicating blood contacting devices [<24 hour contact])*	Acceptable
Ames Mutagenicity of a DSMO Extract	Did not cause mutagenic changes *(Not required for external communicating blood contacting devices [<24 hour contact])*	Acceptable
Ames Mutagenicity of a Saline Extract	Did not cause mutagenic changes *(Not required for external communicating blood contacting devices [<24 hour contact])*	Acceptable

2.2 Electromechanical Studies

The REVELATION® Tx Microcatheter was subjected to physical bench tests to evaluate operational parameters and stress forces required to induce device failure modes. All tests were conducted per "Electrode Recording Catheter Preliminary Guidance" (Massi 1995) and "Cardiac Ablation Preliminary Guidance" (Massi and Zimmerman 1995). All tests were conducted using catheters manufactured according to product specifications, subjected to in-process inspections/tests, followed by radiation sterilization and thermal cycling per Mil Std 202F, Method 107G, Test Condition A. The REVELATION® Tx is not a deflectable catheter and it does not have an open lumen, so joint seal and deflection fatigue testing was not performed. The results demonstrate the design of the catheter is robust and consistent with similar devices for similar indications, where comparison can be made. Unlike "conventional" endocardial RF ablation catheters, the REVELATION® Tx has been designed to provide a more flexible and less traumatic interface with endocardial tissue at its distal tip. The electrical characteristics of the devices were evaluated consistent with IEC 60601-1 and 601-2-2 and found to be compliant with the relevant standards.

The accessory cables and the passive switchbox interface for this system were also tested for reliability and compliance with relevant international standards and found to be compliant. In the case of the switchbox, a third-party evaluation was performed by TÜV Product Services and certification of compliance was issued.

2.2.1 Electrical Performance Testing

Electrical tests were performed on samples from three lots of REVELATION® Tx Microcatheters. The testing of electrode and thermocouple continuity was performed both as part of the standard in-process checks and again following flexural fatigue integrity mechanical testing. Further testing included Dielectric Strength, RF Leakage Current, Impedance, RF Power Coupling, and Stress Induced Noise. All test samples met the defined acceptance criteria both before and after fatigue testing. For all other electrical tests, all test samples met the defined acceptance criteria.

2.2.2 Mechanical Performance Testing

A series of mechanical tests were performed on three lots of REVELATION® Tx Microcatheters. Those tests included Buckle Force, Flexural Rigidity, Flexural Fatigue, Angular Rotation, Torsional Integrity, Tensile Strength, Torsional Rigidity, and Connector Flexural Integrity. The Tensile test includes testing of the distal laminated tip tensile strength and connector-catheter tensile strength. All test samples met the defined acceptance criteria for each mechanical test.

2.2.3 Radiopacity Testing

The characterization of the radiopacity of the REVELATION® Tx Microcatheter was considered consistent with the draft guidance for cardiac ablation devices (Massi, March 1995). However, the only portions of the catheter designed to be radiopaque are the distal tip coil and the electrodes of the REVELATION® Tx, which are platinum. Platinum is known to be a highly radiopaque metal and is commonly used in the construction of catheters for that reason.

The March 1995 Electrode Recording Catheter Preliminary Guidance states that the radiopacity of the compounded tubing should be tested according to Method C of ASTM F 640 Standard Test Methods for Radiopacity of Plastics for Medical Use. The test method requires the formation of a 2mm x 25mm x 150mm slap of the catheter's compounded tubing as the test sample. The fluropolymer jacket covering the length of the REVELATION® Tx Microcatheter is formed from a virgin resin that is not compounded with any radiopaque substance. As a result, the test method is not applicable because 1) the fluoropolymer jacket is not compounded, and 2) the radiopaque portions of the catheter are metallic and not capable of being formed into a slab.

The REVELATION® Tx Microcatheter is to be used with a guiding catheter. Cardima's NAVIPORT and all similar guides are fabricated from compounded radiopaque tubing and have demonstrated their radiopacity. The radiopacity of the REVELATION® Tx's 1 cm long platinum tip and each of the eight 3 mm long electrodes (spanning a length of 4 cm) has been demonstrated in animal and human clinical studies to be sufficient to allow the physician to fluoroscopically guide the device in the right atrium.

3.0 ANIMAL STUDIES

Cardima conducted three prospective studies with 15 animals (7 goats and 8 dogs) to demonstrate performance and safety and to characterize lesion formation, especially in relationship to RF energy delivery. The studies indicated that the REVELATION® Tx Microcatheter Ablation System was capable of creating continuous, linear transmural lesions, that a continuous lesion can be formed from sequential electrode ablations; that a set temperature of 50°C-55°C at 35W maximum power output were the best procedural parameters for minimal coagulum formation and optimal lesion formation. These studies also demonstrated that a low pre-ablation pacing threshold was an indicator of good tissue contact and that a large increase in the pacing threshold was a good indicator that lesions had been formed. There were no device-related complications in any of these studies. No correlation between RF energy delivery parameters and lesion size and location could be clearly identified. The study details are summarized in **Table 3**.

There was also one external study of the REVELATION® Tx Microcatheter Ablation System with 10 dogs.[22] The results of this prospective study demonstrated that the REVELATION® Tx (referred to in the article as MICRO) could be successfully used to create continuous, linear RF lesions in the right atrium.

TABLE 3
REVELATION® Tx Animal Studies

Study	Objectives	Investigator	N	Outcome
Performance of REVELATION® Tx in Right Atrium of Goat (#97-010-FL)	Assessment of device performance, lesion formation and depth with single placement in beating heart of 3 acute and 4 sub-chronic (1-4 weeks) goats. Includes measurement of pacing thresholds, electrogram signal quality, and thrombus/coagulum formation.	David Keane, PhD, MD, Massachusetts General Hospital (9/97)	7	• No catheter-related complications occurred. • Contiguous, transmural lesions were occasionally obtained. The catheter was placed only once on the different regions of the heart. • Coagulum was generally absent on electrodes at 45ºC and 50º0C. • An upper power limit of 25W in this study showed good control of thrombus formation. • Low pre-ablation pacing threshold was an indicator for good tissue contact. • Large increase of pacing threshold post-ablation was an indicator of achieved lesions in the heart.
Performance of REVELATION® Tx in Right Atrium of Canine (97-013-FL)	Assessment of deployment, lesion creation, and device performance with single placement (no re-positioning) at predetermined locations and predefined control set temperatures in the beating heart of 2 acute and 4 sub-chronic (1 week) dogs. Confirmation of goat study in different cardiac morphology.	Mauricio Arruda, MD, University of Oklahoma (10/17/97)	6	• No significant catheter placement difficulties in the IVC-SVC or subeustacian isthmus regions. • Contiguous, transmural lesions were obtained (including in the isthmus with a superior approach). • Bipolar and unipolar electrograms were typically of good quality without significant noise. • Minimal coagulum observed on some electrodes. • Recommended temperature set range (based on this study) is 50ºC-55ºC.
RF Lesion Formation in Canine Thigh Muscle (#97-012-FL)	Assessment of lesion size and thrombus formation in 28 lesions created in 2 dogs.	Maruricio Arruda, MD, University of Oklahoma (10/22/97)	2	• Continuous lesion was formed from sequential electrode ablations. • In the absence of blood flow, creation of lesions at 45ºC may be ineffective. Charring may occur at 60ºC. • Thrombus was not observed when 45C was used, occasionally at 50ºC and 55ºC. • High blood flow around the electrode allowed more RF power delivery and correlated with deeper and wider RF lesions

4.0 PHASE IIA FEASIBILITY STUDY

In 1997, a 10 patient feasibility study (Phase IIa) was conducted to assess initial safety and effectiveness of the REVELATION® Tx Microcatheter Ablation System in humans. Patients over the age of 21 and less than 75 years of age with paroxysmal atrial fibrillation who were drug-refractory to at least 2 AADs and had at least one symptomatic episode during a month long baseline monitoring period were eligible. Patients received up to three right atrial lesions (septal, lateral, and an optional anterior line) with the REVELATION® Tx Microcatheter and received isthmus lesions with another catheter of the physician's choice. The primary study endpoint was procedure safety. Secondary endpoints included patients reporting an absence or reduction in frequency and/or duration of any spontaneous episodes of AF at 6 months. The study results demonstrated that the REVELATION® Tx Microcatheter Ablation System could be used safely to create right-sided linear lesions and 4/10 patients had 50% or greater reduction in number of symptomatic AF.

5.0 PHASE IIB CLINICAL STUDY

5.1 Study Design

The Phase IIb clinical study was approved under IDE G970280/S39 on August 18, 2000. It was a single-arm, prospective multi-center study that enrolled 38 patients at 9 centers for the treatment of drug-refractory paroxysmal atrial fibrillation with the REVELATION® Tx Microcatheter Ablation System with optional use of the NAVIPORT guide catheter.

The study objective was to demonstrate the safety and effectiveness of the REVELATION® Tx Microcatheter Ablation System to map, pace and create linear lesions in the right atrium of patients with drug refractory symptomatic paroxysmal atrial fibrillation. The primary endpoint was a reduction in symptomatic AF episode frequency from baseline to 6 months of 50% greater.

Patients over the age of 21 and less than 75 years of age with paroxysmal atrial fibrillation who were drug-refractory to at least 2 AADs and had more than 2 symptomatic episodes during baseline monitoring were eligible for the study.

5.2 Study Results

Thirty-eight (38) patients were treated with the REVELATION® Tx Microcatheter Ablation System to create a pre-specified right atrial lesion set (septal, lateral, and an optional anterior line). For the isthmus lesion, the investigator used his choice of a single-tip catheter. These study results were included as part of the study population in the first clinical PMA submitted by Cardima on September 2, 2003.

The majority of Phase IIb subjects (27/31, 87%) transmitted transtelephonic event recordings that demonstrated a reduction in episode frequency from baseline in the first month after ablation. **Table 4** depicts the results from those subjects. At six months, 100% of the subjects demonstrated some reduction in symptomatic episodes. At the six-month endpoint, 18/21 patients had 50% or greater reduction in the number of symptomatic AF episodes.

TABLE 4
Summary of Symptomatic AF Episode Reduction from Baseline

Criterion	1 Month	3 Month	6 Month
# of subjects with episode reduction compared to baseline	27/31 (87%)	29/31 (93.6%)	21/21 (100%)
≥50% Reduction	18/31 (58%)	23/31 (74.2%)	18/21 (86%)
≤50% Reduction	9/31 (29%)	6/31 (19.4%)	3/21 (14%)
No Reduction	3/31 (10%)	1/31 (3%)	0/21 (0.0%)

The adverse event rate during the Phase IIb study was low. In total, 1 of 38 (2.6%) subjects experienced a perioperative serious adverse event (stroke). The safety profile was sufficient to justify performance of a larger Phase III clinical study. The larger Phase III clinical study was developed under an almost identical protocol (see description below) to permit pooling of the data.

6.0 CLINICAL STUDY DESIGN

6.1 Summary

The REVELATION® Tx Microcatheter Ablation System clinical investigation was a non-randomized single-arm clinical trial with a before-after design. Subjects with drug-refractory, symptomatic, paroxysmal AF who experienced three or more episodes during a baseline 30-day monitoring period were included. Subjects were followed for two years. The pivotal trial met the pre-specified success endpoints. The full study protocol is included in **Appendix A** of the Sponsor Panel Pack.

6.2 Objectives

The purpose of the study was to assess the safety and effectiveness of the REVELATION® Tx Microcatheter Ablation System in the treatment of subjects with drug refractory paroxysmal AF by creating linear lesions with RF energy in the right atrium.

6.3 Endpoints and Rationale

The primary effectiveness endpoint was: frequency of any spontaneous symptomatic episodes of AF experienced by the subject. The primary safety endpoint was the incidence of adverse events.

The definition of clinical success for the primary effectiveness endpoint was based on an inverse scale of percentage episode reduction in episodes in the sixth month versus baseline level of number of episodes. For subjects with ≥5 episodes during the 30-day baseline period, a reduction of 50% or more was required to constitute a clinical success. For those subjects with 3-4 episodes during the baseline period, a reduction of 75% was required to constitute a clinical success.

An additional clinical success endpoint was defined as either a 50% or 75% reduction in symptomatic AF episodes while either maintained on the same anti-arrhythmia drug regimen or a reduced dosage.

The secondary endpoint was quality of life, based upon an evaluation of the subjects' responses to general quality of life as queried in the Medical Outcomes Trust Short Form 36 (SF-36) and on the symptoms and severity of their AF episodes as described in the Atrial Fibrillation Severity Scale (AFSS), both of which are validated and accepted instruments for measuring these outcomes.

A change of ten points or more per category between the sixth month of follow-up and the baseline values was considered clinically significant. Statistical significance for all outcomes was based upon the results of statistical analysis of change from baseline.

The procedural endpoint was a reduction in post-ablation amplitudes relative to pre-ablation. This endpoint success was measured by demonstration at the line(s) of ablation during sinus rhythm at least one of the following: a) reduction in the amplitude, fragmentation or widening of local electrograms or b) appearance of split potentials.

6.4 Subject Population

Subjects were drawn from the general population diagnosed with AF. This study targeted those subjects with documented drug refractory symptomatic paroxysmal AF episodes who were referred to a participating electrophysiologist by their treating physician or cardiologist.

6.4.1 Inclusion Criteria

- Diagnosis of paroxysmal atrial fibrillation (PAF)
- Refractory to at least two (2) AADs (unless one is amiodarone, then no 2nd AAD is required)
- Documented three (3) or more symptomatic AF episodes during the 30 day baseline monitoring period
- At least 21 years of age and not more than 80
- Signed an IRB-approved informed consent
- Ability and willingness to comply with protocol
- Normal sinus rhythm (NSR) at the time of the procedure or can be converted to NSR

6.4.2 Exclusion Criteria

- Pregnancy
- Prior acute ablation failure within the previous two months
- Myocardial infarction within the prior six weeks
- Contraindication or an inability to comply with long-term anticoagulation therapy
- Significant underlying structural heart disease (defined as valvular disease, presence of aneurysm or left ventricular hypertrophy) with function New York Heart Association Classification of Class III or IV
- Known or suspected coagulopathy or bleeding diathesis
- History of prior cardiovascular accident (CVA) or transient ischemic attack (TIA)
- Presence of intracardiac thrombus (determined by TEE)
- Evidence of a patent foramen ovale or atrial septal defect (determined by TEE)
- Atrial dimension of > 5.0cm
- Any condition that, in the investigator's opinion, would place the subject at an increased risk for complications

6.4.3 Recruitment

Recruitment was at the discretion of investigators, but primarily occurred via referral from cardiologists and internists to study investigators, all of whom were experienced electrophysiologists located at academic and non-academic medical centers in the U.S.

6.5 Follow-up Assessment

The study protocol required two years of follow-up, including an initial six-month post procedure period during which subjects record symptomatic AF episodes and transmit weekly during the first through third month and again during the sixth month post treatment. For convenience, subjects may record and transmit continuously through the 6 month follow-up period, but only data from month three and month six are used to calculate episode reduction. Office visits are required at 1, 3, 6, and 12 months that included a physical examination, TTE, EKG and reports of any complications or adverse events that had occurred during the assessment interval. A telephone contact follow-up was required at 24 months to establish the status of the subject (alive) and the incidence of any adverse events. Required study assessments are listed in **Table 5**.

TABLE 5
Required Study Assessments in the Phase III REVELATION® Tx Microcatheter Ablation System Clinical Investigation

Examination	Baseline	Prior to hospital discharge	Month				
			1 (± 2 wks)	3 (± 2 wks)	6 (± 4 wks)	12 (± 4 wks)	24 (± 6 wks)
Medical History	X						
Physical Examination	X	X	X	X	X	X	
Stress test	X			X			
12 Lead EKG	X	X	X	X	X		
Transesophageal Echocardiogram	X						
Transthoracic Echocardiogram		X		X			
PT/PTT INR	X	X	X	X			
Medication Review	X	X	X	X	X	X	X
Arrhythmia Events	X		X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Quality of Life Questionnaires	X			X	X		
Urine or Serum Pregnancy Test (if applicable)	X						
Cardiac Event Monitor	X	X	X	X	X		
Telephone Interview							X

6.6 Pre-Enrollment Baseline Testing

At baseline, each subject was required to monitor symptomatic episodes using the cardiac event monitor for a 30-day period. The monitoring service provided study sites with weekly event logs, including all rhythm strip information, for review. Investigators and site coordinators reviewed these data with the subject at the end of the 30-day baseline period. Each subject was required to have experienced and recorded at least three episodes of investigator-confirmed symptomatic AF during the baseline period in order to qualify for the RF ablation procedure. Subjects were not made aware of this threshold. The monitoring service's independent cardiologist reading, which was not available in real time, was not used to help the investigator determine whether a subject qualified for ablation.

Potential study subjects were allowed to "re-screen" for the baseline if less than three symptomatic episodes were captured and transmitted at the end of the 30-day monitoring period. A "re-screen" subject was required to monitor episodes for an additional 60 days to collect a total of 90 days of event monitoring. The number of symptomatic episodes required for a re-screen subject to be considered eligible was a total of nine episodes in order to maintain the same frequency required for the initial period (3 episodes/30 days).

Quality of life was assessed at baseline and follow-up periods using two instruments: the SF-36 and the AFSS.

At the conclusion of the baseline monitoring period, subjects were determined eligible for treatment if they met all of the eligibility criteria.

6.7 Study Procedure

Study subjects were treated by the placement of linear lesions in the right atrium to form lines of block from one anatomical barrier to another. Subjects taking Coumadin discontinued its use three days prior to the procedure. Heparin was administered at the investigators' discretion.

Ablation took place under conscious sedation or general anesthesia in the electrophysiology laboratory. Through femoral vein access, the REVELATION® Tx Microcatheter was used to create linear lesions in the posteroseptal and lateral regions of the right atrium. Lesions were created at a set temperature of 50º C, a maximum power of 35 W, and maximum impedance of 200 ohms for a total of 60 seconds per electrode. Decreases in atrial wave amplitudes were monitored during the procedure. In addition, the cavotricuspid isthmus region was ablated using either the REVELATION® Tx or the NAVABLATOR® ablation catheter. If bidirectional conduction block at the isthmus line could not be demonstrated using the Cardima catheters, use of another ablation catheter per the site's standard practice was allowed. Subjects were monitored for complications and hospitalized overnight.

6.8 Adverse Events

All adverse events experienced by study subjects were documented and have been appropriately reported. Site investigators were required to make a determination of whether the event was probably or possibly related to the device, or not related.

The REVELATION® Tx Microcatheter Ablation System clinical investigation used the FDA definition of a major complication/serious adverse event[23] as the definition of complication. FDA defines a major complication as an adverse event which "occurs within the first week following the investigational procedure and:

- is life-threatening; or
- results in permanent impairment of a body function or permanent damage to a body structure; or
- necessitates significant intervention, such as major surgery, to prevent permanent impairment of a body function or permanent damage to a body structure; or
- requires hospitalization or an extended hospital stay; o
- results in moderate transient impairment of a body function or transient damage to a body structure; or
- requires intervention such as medication or cardioversion to prevent permanent impairment of a body function or damage to a body structure."

Serious adverse events meeting all but the timing criteria of the SAE definition were also recorded.

6.9 Statistical Methods

Standard frequentist statistical methods were used throughout. For continuous variables, (paired) t tests and ANOVA were used for comparisons of means. For categorical variables, standard tests of proportions were used, including chi squared tests, where appropriate. Confidence intervals were calculated using standard formulas. For continuous variables, 1.96 $\pm$ SE was used; for binary variables, the exact binomial distribution was used. Changes in the proportion of subjects with symptoms from baseline to six months were evaluated with McNemar's test. In situations where outcomes were thought to be clustered, hierarchical or mixed random effects regression was performed (e.g., PROC MIXED).[24] Continuous variables were log-transformed, where appropriate, to improve "normality."

6.10 Methods to Reduce Study Bias

The trial was unblinded, and therefore design features were implemented to reduce the potential for bias:

- Rhythm strips were evaluated by independent cardiologists.
- Subjects were blinded to the number of episodes required to qualify for the study during the baseline monitoring period.
- Subjects were generally unaware, throughout the study, of monitoring service's and independent cardiologist's interpretations of rhythm strips.

7.0 CLINICAL STUDY RESULTS

7.1 Study Sites

Twenty-three (23) sites enrolled subjects in the study. Three of them withdrew, at Cardima's request, because they were not successful in enrolling study subjects. The study sites and their principal investigators are listed in **Table 6**.

7.2 Subject Enrollment by Site

Ninety-three (93) subjects undergoing 95 procedures comprised the procedure cohort. Subject enrollment by site is depicted in **Table 6**.

TABLE 6
Subject Enrollment By Site

Principal Investigator	Clinical Investigational Site	Study Phase	Subjects per Site
Ruey J. Sung, MD	Stanford Medical Center Stanford, CA	I (IIa)	3
Sung H. Chun, MD		III	0
Jeremy N. Ruskin, MD	Massachusetts General Hospital Boston, MA	I (IIa)	3
David Keane, MD		II, III	2
Hugh Calkins, MD	The Johns Hopkins Hospital Baltimore, MD	I (IIa)	4
		II, III	6
Douglas L. Packer, MD	Mayo Clinic Rochester, MN	II	1
Ted D. Friehling, MD	Inova Institute for Research and Education Falls Church, VA	II, III	15
Roger A. Marinshak, MD	Main Line Health Heart Center Wynnewood, PA	II, III	11
Douglas B. Esberg, MD		III	0
David J. Wilber, MD	University of Chicago Chicago, IL	II	2
Bruce G. Hook, MD	New England Heart Institute Manchester, NH	II, III	4
Seth J. Worley, MD	Lancaster Heart Foundation Lancaster, PA	II, III	4
Timothy M. Talbert, MD	Diagnostic Center of CV Diseases Chattanooga, TN	II, III	14
Sanjeev Saksena, MD	EHI-Atlantic Health System Cardiac Medicine & Electrophysiology	III	4

Principal Investigator	Clinical Investigational Site	Study Phase	Subjects per Site
	Warren, NJ		
David Fitzgerald, MD	Wake Forest University Winston-Salem	III Withdrawn	0
Gregory Feld, MD	UC San Diego Medical Center San Diego, CA	III Withdrawn	0
Abraham G. Kocheril, MD	Carle Heart Center Urbana, IL	III	14
Larry A. Chinitz, MD	NYU Medical Center New York, NY	III	1
Imran K. Niazi, MD	Wisconsin Center for Clinical Research, St. Francis Hospital Milwaukee, WI	III	11
	Wisconsin Center for Clinical Research, St. Luke's Hospital Elkhorn, WI		
Jose Nazari, MD	Cardiac Arrhythmia Consultants Chicago, IL	III	2
Randy A. Lieberman, MD	Harper University Hospital Detroit, MI	III	4
Roger A. Winkle, MD	Sequoia Hospital Redwood City, CA	III	3
Kara Quan, MD	MetroHealth Cleveland, OH	III Withdrawn	0
Eli S. Gang, MD	Access Clinical Trials Beverly Hills, CA	III	1
Bruce B. Lerman, MD	Cornell University New York, NY	III	0
Arjun D. Sharma, MD	Regional Cardiology Associates Sacramento, CA	III	0
Total			109

7.3 Baseline Characteristics

The recruited study population had baseline medical characteristics and concomitant conditions consistent with expectations for subjects with paroxysmal AF. The recruited population appeared to meet the Agency's recommendations that subjects be highly refractory to standard medical treatment for AF.

7.3.1 Demographic Characteristics

In the procedure cohort, 93 Phase III subjects underwent RF ablation with the REVELATION® Tx Microcatheter Ablation System. Mean subject age was 58 years (range 28 to 78) (**Table 7**). Seventy-four percent of subjects were male, and men were slightly younger.

TABLE 7
Descriptive Statistics for Age by Gender

	Age						
	Frequency	**%**	**Mean**	**Std**	**Min**	**Median**	**Max**
Gender							
Female	24	25.8	62.2	9.8	42	63	77
Male	69	74.2	56.8	10.0	28	58	78
Total	93	100.0	58.2	10.2	28	59	78

7.3.2 Medical Characteristics – Cardiovascular Disease

Sixty-nine (76%) subjects had some form of concomitant cardiovascular disease; however, due to exclusion criteria and screening, study subjects did not have significant structural heart disease. **Table 8** provides details of prior cardiac interventions. Thirty subjects (32%) had previous RF ablation procedures; 24 were for atrial flutter, seven for AF and four for other indications.[b] On average, subjects reported a history of symptomatic AF for five years (range < 1 year to > 8 years, **Table 9**).

TABLE 8
Details of Previous Cardiac Interventions (N=93)

Type of Intervention	Frequency*	%
No Prior Cardiac Interventions	71	76.3
RF Ablation	30	32.3
DC Cardioversion	7	7.5
Pacemaker	6	6.5
CABG	10	10.8
Angioplasty/Stent	6	6.5

*Some subjects had more than one prior cardiac intervention

[b] Values do not sum to 30 because some subjects had dual indications.

TABLE 9
Duration of AF Prior to Ablation (N=93)

Duration of AF (years)	Frequency	%
< 1 year	17	18.3
1 to 2 years	10	10.8
2 to 3 years	11	11.8
3 to 4 years	14	15.1
4 to 5 years	2	2.2
5 to 8 years	17	18.3
> 8 years	22	23.7

7.3.3 EKG Findings at Baseline

EKG findings were common at baseline, which was not unexpected given the study recruitment criteria (see **Table 10**). AF was present in 23 (25%) subjects and conduction abnormalities were common.

TABLE 10
EKG Findings at Baseline (N=93)

Finding	Frequency	%
Rhythm		
Normal sinus rhythm	40	43.0
Sinus bradycardia	23	24.7
Premature atrial contractions	3	3.2
Atrial tachycardia	1	1.1
Atrial fibrillation	23	24.7
Atrial flutter	3	3.2
Unifocal PVCs	3	3.2
Paced	6	6.5
Conduction		
Normal	59	63.4
First degree block	3	3.2
Right bundle branch block	3	3.2
Left bundle branch block	2	2.2
IRBBB	2	2.2
Intraventricular conduction delay	3	3.2
ST-T wave abnormalities	15	16.1
Other	14	15.1
Morphology		
Normal	84	90.3
RA hypertrophy	1	1.1
LA hypertrophy	2	2.2
RV hypertrophy	1	1.1
LV hypertrophy	1	1.1
Other	4	4.3

7.3.4 Medical Characteristics – Other Disease

Other concomitant disease was fairly common among study subjects (**Table 11**). Thirty-three percent (33%) had respiratory disease, 30% had endocrine disease and 45% had musculoskeletal disease.

TABLE 11
Frequency of Concomitant Baseline Medical Disease (N=93)

Medical History	Frequency	%
Respiratory	31	35.5
Endocrine	28	32.3
Renal	20	23.7
Neurological	21	24.7
Hematopoetic	2	2.2
Lymphatic	1	1.1
Musculoskeletal	42	48.4
Gastrointestinal	38	44.1
Immunologic	5	5.4
Psychological	9	10.8

7.3.5 Baseline Cardiac Status

Functional Status

All subjects had good cardiovascular functional status, as indicated by New York Heart Association (NYHA) class ratings of I in 68 subjects (74%) and II in 24 subjects (26%) (**Table 12**).

TABLE 12
Baseline NYHA status (N=92*)

NYHA Classification	Frequency	%
I	68	73.9
II	24	26.1

*Value not completed by one study investigator. According to the investigator, the subject had good overall cardiovascular status. The NYHA question was not answered since it was perceived to be "not relevant" for subjects without heart failure.

Despite good functional status, subjects reported frequent occurrence of symptoms related to AF at baseline (**Table 13**). Eighty-eight percent (88%) had palpitations, 58% fatigue, 49% shortness of breath, 36% lightheadedness and 21% chest pain.

TABLE 13
Baseline Symptoms of AF Episodes (N=93)

Symptom	Frequency	%
Palpitations	82	88.2
Fatigue[a]	53	57.6
Shortness of breath[a]	45	48.9
Lightheadedness[a]	33	35.9
Chest pain[b]	19	20.9

a) 1 response missing
b) 2 responses missing

Baseline Symptom Episode Frequency

Table 14 provides the distribution of baseline symptomatic episodes recorded using cardiac event monitors. Subjects with fewer than three episodes at baseline were not qualified to undergo RF ablation in this study. Twenty-seven (27) subjects (29%) had 10 or more episodes at baseline; 11 (12%) had 20 or more at baseline. The mean (±SD) number of episodes at baseline was 9.7 ± 9.2.

TABLE 14
Distribution of Symptomatic AF Episodes That Occurred During the Baseline 30-Day Monitoring Period

Baseline Episodes	Frequency	%
3	15	16.1
4	14	15.1
5	8	8.6
6	12	12.9
7	4	4.3
8	5	5.4
9	8	8.6
10 to 14	9	9.7
15 to 19	7	7.5
20 to 29	7	7.5
30+	4	4.3
Total	93	100.0

7.3.6 Baseline Quality of Life

Quality of life was assessed at baseline and follow-up periods using two instruments: the SF-36) and the AFSS.

SF-36 Scores

Table 15 provides a comparison of baseline SF-36 scores between trial subjects and the general US population. Compared to the general US population, REVELATION® Tx Microcatheter Ablation System trial participants showed substantially lower physical and vitality scores, consistent with the presence of symptomatic AF and a meaningful impact of AF on physical health.

TABLE 15
Comparison of SF-36 Scores in Cardima Clinical Trials to Other Literature

SF-36 Scale	General US Population Scores [c]		REVELATION® Tx Study Baseline		
	Mean	SD	N[a]	Mean	SD
Physical Functioning	84.2	23.3	89	70.3	25.5
Role Physical	80.9	34.0	91	41.2	43.2
Role Emotional	81.3	33.0	90	65.6	39.5
Bodily Pain	75.2	23.7	92	71.0	23.6
General Health	71.9	20.3	91	63.3	20.6
Vitality	60.9	20.9	92	46.9	21.9
Social Functioning	83.3	22.7	92	70.7	26.9
Mental Health	74.7	18.1	92	74.0	16.9

a) Baseline responses missing in 1 to 4 subjects across dimensions

Atrial Fibrillation Severity Scale

AFSS scores were determined at baseline and in follow-up using an adapted version of Dorian's original instrument.[25] **Table 16** provides descriptive statistics for scores for each question, adjusted to a 0-to-100 scale (higher scores indicate better health).

[c] See US Population Norms, 1998, at http://www.sf36.com

TABLE 16
Baseline AFSS Scores by Study Phase

AFSS Dimension	N	Mean	Std
Episode Frequency	92	32.7	19.2
Episode Duration	91	43.6	25.9
Episode Severity	92	49.0	23.4
Total AFSS	91	41.3	14.7

Given that normative ranges are unavailable, these baseline findings were interpreted as showing that study subjects had frequent episodes of arrhythmia of moderate duration and of medium severity.

7.3.7 Medications at Baseline

To qualify for ablation, subjects were required to have drug-refractory, symptomatic paroxysmal AF. Drug-refractory was defined as lack of clinical response, as judged by the investigator, to two or more AADs or to amiodarone alone. The requirement for drug refractoriness, which was consistent with the 1998 FDA Advisory panel recommendations for clinical trials of device-based treatment for AF, ensured that subjects had exhausted all standard therapies before undergoing the investigational procedure. On average, subjects were refractory to 2.9 AADs (median 3). Medications to which subjects were refractory are shown in **Table 17**. Thirty-eight (38) of 93 subjects (41%) had tried and failed amiodarone.

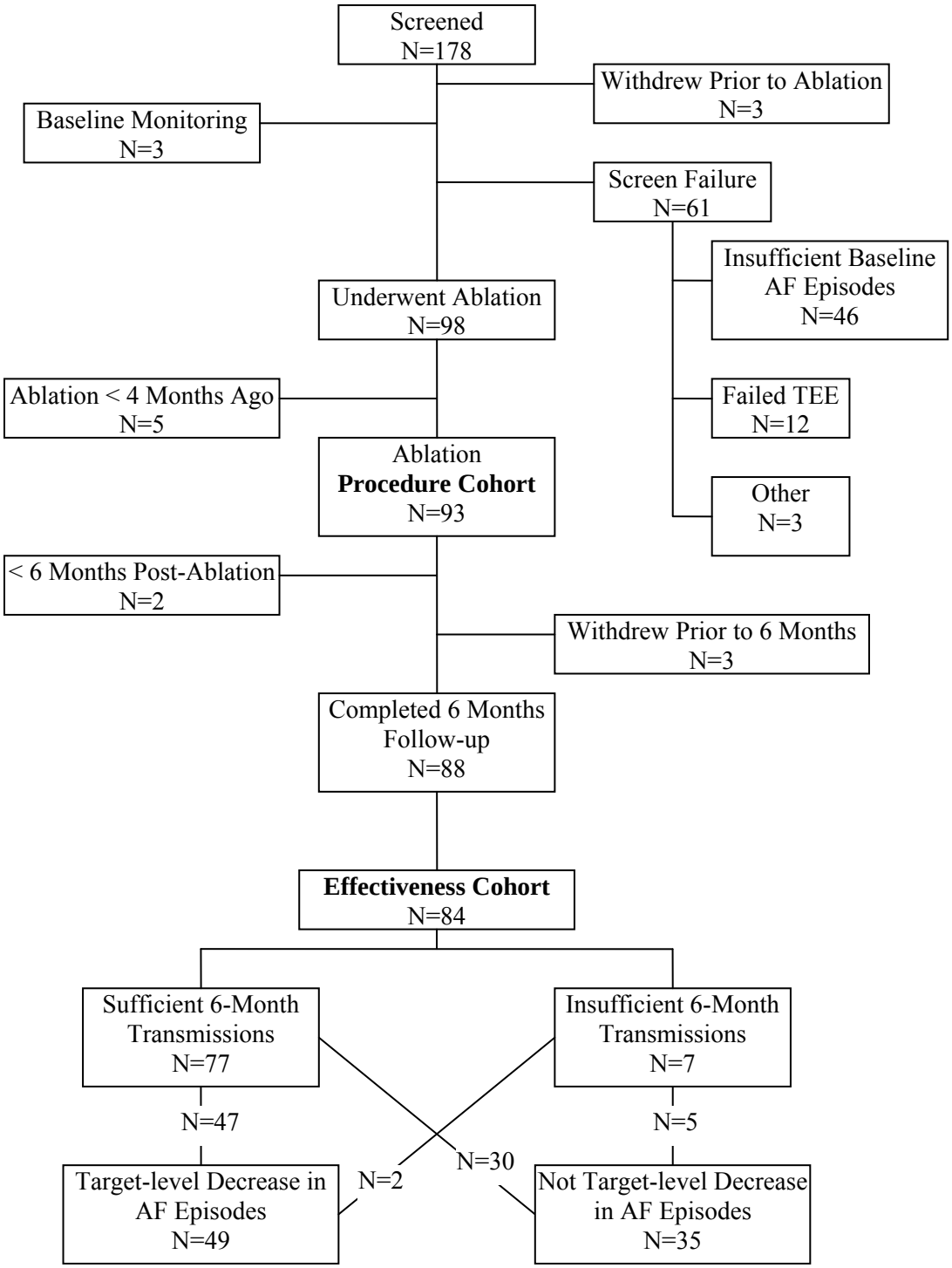
TABLE 17
Generic Drug Names to Which Subjects Were Refractory at Baseline

Drug name	Frequency
Amiodarone	38
Atenolol	19
Azimilide	2
Bisoprolol	1
Digoxin	24
Diltiazem	26
Disopyramide	8
Dofetilide	11
Flecainide	20
Metoprolol	15
Mexilitine	1
Moricizine	1
Procainamide	6
Propafenone	31
Propranolol	1
Quinidine	7
Sotalol	45
Verapamil	10

7.4 Subject Flow Chart

As of December 10, 2003, 178 subjects had been screened for trial participation. Sixty-one subjects failed screening, 46 due to insufficient symptomatic AF episode counts, 12 due to findings on transesophageal echocardiography (mostly left atrial size > 5 cm and rarely thrombus or patent foramen ovale) and three for other reasons. Sixteen subjects withdrew prior to ablation. In all, 93 Phase III subjects undergoing 95 procedures comprised the procedure cohort, i.e., the group of study subjects in whom procedure and safety analyses were performed.

FIGURE 1
Subject Accountability



Of the 93 subjects in the procedure cohort, 3 withdrew from the study prior to the six-month study endpoint, and 4 withdrew after the six-month endpoint.

7.5 Procedural Results

Ninety-three (93) subjects underwent ablation procedures with the REVELATION® Tx Microcatheter Ablation System. Mean (SD) procedure time was 218 (111) minutes; mean investigational catheter time was 162 (74) minutes; mean fluoroscopy time was 43 (42) minutes. There was modest variation of procedure, investigational and fluoroscopy time across study sites. However, such variation was expected due to use/non-use of different mapping techniques, and the use of different baseline electrophysiologic testing procedures, both of which were allowed by the study Protocol. Across sites, maximum procedure times ranged from 131 to 549 minutes.

7.5.1 Posterolateral and Septal Lesions

The July 1998 Advisory Panel meeting on the design of clinical trials of AF noted that no acute physiologic endpoint existed for AF procedures that denoted the achievement of a specific outcome indicating that the procedure was complete. Acknowledging this, the study Protocol required investigators to document a proxy measure: reduction of the amplitude of atrial electrogram amplitudes after ablation. Standard procedural endpoints used with single-electrode catheters in left-sided procedures are not applicable a linear, right-sided ablation either. The protocol required documentation of paired before- and after-ablation measurements for each electrode for each lesion created.

Amplitude reductions were measured in 83 of 95 (87%) procedures performed in Phase III. On occasion, before-after measurements were not paired by electrodes; in all, 74 of 95 (78%) procedures had electrode-paired measurements. Using a hierarchical mixed model regression approach, mean reduction in log amplitude (mV) was 0.36, indicating that, on average, measurements made after the ablation were 44% (i.e., $10^{-0.36}$) as large as those prior to ablation, demonstrating that ablations using REVELATION® Tx resulted in a substantial (56%) decrease in atrial electrogram amplitudes.

The reduction in amplitude measurement as a proxy procedural endpoint has limitations. Before-after measurements of atrial amplitudes may be inaccurate and are likely to underestimate the true amount of amplitude reduction caused by ablation since a slight movement of the electrode, change in the mass of atrial tissue in contact with the electrode, or endocardial conduction velocity near the electrode can alter the measurements. Second, the target of ablation is substrate modification and the creation of lines of block using a multi-electrode catheter. At the time of trial design (and arguably today), there was no accepted measurement for determining whether a line of block has occurred.

Amplitude measurements provide strong evidence that, 1) investigators complied with the electrical amplitude measurement aspect of the study protocol despite its lack of perceived utility, and 2) substantial reductions in amplitudes at created lesions were observed. Whether such reductions indicated that the procedure had reached a physiologic endpoint is not known; moreover, whether reductions were predictive of long-term outcome was not determined.

7.5.2 Isthmus Lesion

The protocol required ablation of the cavotricuspid isthmus in order to prevent atrial flutter in follow-up. In Phase III, the NAVABLATOR®, a single-tip catheter that produces lesions similar to other single-tip catheters, was added as an optional catheter for the isthmus line. If the REVELATION® Tx or NAVABLATOR® catheters could not be used successfully to ablate the isthmus, the Protocol permitted the use of standard institutional procedures to complete the isthmus line.[d]

Eighty-nine (89) patients received an isthmus line ablation for the prevention of post-ablation atrial flutter. Six (6) patients had isthmus line ablations prior to the study and were not re-ablated during the procedure in which REVELATION® Tx ablation was performed. Of the 89 patients, eight (8) patients had the isthmus lesion created by the REVELATION® Tx and 51 had the isthmus lesion created only by the Cardima's NAVABLATOR® catheter. In some cases, bidirectional conduction block was not achieved with study-related catheters alone. Thus, four (4) patients had other (non-Cardima) catheters used to create the lesion, and 26 patients had some combination of either of the Cardima catheters and/or another type of catheter used to complete the isthmus lesion.

Please refer to **Appendix C** for further discussion of isthmus ablation and the NAVABLATOR®.

[d] The protocol stated on page 23: "The NAVABLATOR® catheter is optionally available for ablation of the isthmus only after first attempting to create a linear burn with the REVELATION® Tx. An alternate line may be made from the CS to the TA provided conduction block can be shown to naturally exist along the eustacian ridge from the IVC to the CS. Additional RF delivery between the eustacian ridge and the TA may also be performed if necessary to insure conduction block. If bi-directional conduction block cannot be obtained with the above procedure, the physician should complete the isthmus trajectory using standard institutional procedures." Please refer to **Appendix A** for the full protocol.

7.6 Endpoints

7.6.1 Primary Endpoints

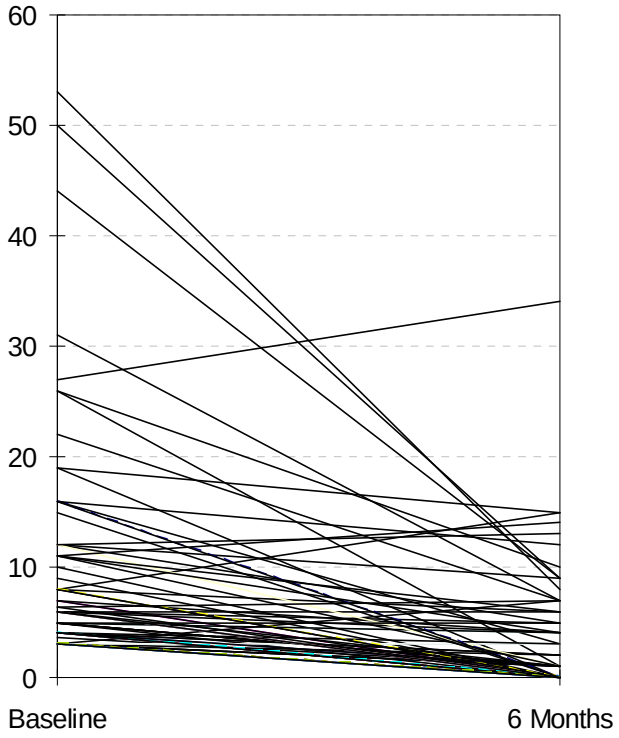
Episode Reduction

At baseline, subjects who completed six months of follow-up experienced a mean of 9.5 episodes of symptomatic AF per month (**Table 18**). At three and six months, symptomatic AF episode counts were reduced to 3.7 and 3.4 episodes per month, respectively; the mean per-subject six-month reduction in symptomatic AF episode counts was 62.3% ($p<.0001$, paired t test). The 95% confidence interval for the percent episode reduction was 50.6 – 73.1. **Figure 2** shows a per-subject plot of baseline and six-month symptomatic AF episode counts.

TABLE 18
Mean Baseline, 3-Month, and 6-Month Symptomatic AF Episode Counts, and Six-Month Percent Reduction in Symptomatic AF Episodes

Period	N	Mean (SE)
Baseline	84	9.5 (1.1)
Three month	82	3.7 (0.6)
Six month	77	3.4 (0.6)
Reduction at six months (%)	77	62.3 (5.4)

FIGURE 2
Per-Subject Plot of Change in Episode Count from Baseline to Six Months
(N=77)



Subjects not transmitting any rhythm strips at six months were not included in the figure.

Target-Level Symptom Reduction

As per the protocol, reductions in symptomatic AF episode counts were categorized as meeting or not meeting the target-level decrease according to the baseline number of episodes experienced. To be considered a success, subjects with three or four episodes at baseline needed to experience a reduction of 75% or more during the sixth month of the monitoring period, and subjects with five or more episodes at baseline needed to experience a reduction of 50% or more during the sixth month.

In all, 47 of 84 (56%) subjects in the effectiveness cohort achieved the target level decrease. Among the seven subjects with no six-month transmissions, two were also considered clinical successes (patients 1418 and 1702), as manifested by verbal comments and marked improvements in AFSS episode frequency score. Including these two subjects as successes, the overall success rate was 49 in 84 (58%, 95% CI 48 - 68%). The width of the confidence intervals (± 10%) is in accord with the study protocol's sample size calculation. Note that, but for the two noted exceptions, all success rate calculations consider those with zero six-month transmissions to be failures. Among the 49 successes, 14 occurred among 29 subjects with 3 to 4 episodes at baseline and 35 occurred among 55 subjects with five or more episodes at baseline (**Table 19**).

TABLE 19
Target-Level Episode Reduction by Baseline Episode Counts

Baseline Symptomatic AF Episodes	Episode Reduction Success	
	s/n	%
3 to 4	14/29	48.3
5 or more	35/55	63.6
Total	49/84	58.3

s = successes, n = number of subjects in subgroup

Among those subjects who did not achieve the target-level reduction in episode counts, the mean (SE) percent reduction in episode counts was 17 (8.4).

Table 20 provides a summary of the six-month symptomatic episode reduction in the REVELATION® Tx Microcatheter Ablation System investigations. The mean reduction in episode counts was 62%, with 79% of subjects having lower episode counts at six months of follow-up compared to baseline. Fifty-eight percent achieved the target level reduction, and over one-third of the subjects (35%) were episode free.

TABLE 20
Summary of Six-Month Symptomatic AF Episode Reductions from Baseline (N=84)

	6 Month Summary
Mean % reduction ± SE (95% CI)[a]	62.3% ± 5.4 (50.6 – 73.1)
Target-level (>75%/50%) reduction (95% CI)[b]	49/84 (58.3%, 47.6 – 68.3%)
At least some episode reduction compared to baseline	66/84 (78.6%)
100% reduction	29/84 (34.5%)
No reduction or increase	11/84 (13.1%)

a) Excludes 7 non-compliant subjects
b) Includes two subjects with marked improvements on AFSS question 5

Complications

Investigators reported a total of 50 adverse events among 22 subjects (24%) in the procedure cohort that were possibly or probably related to the device and/or the procedure. The majority of complications were reported to be possibly related to the procedure rather than the device. Nine (9) of the 22 subjects (41%) with AEs were reported at a single site; this site accounted for 28 (56%) of the 50 total events. Consequently, the likelihood that a subject was reported to have experienced an AE varied across study sites, possibly due to investigators having different thresholds for reporting AEs, so the 24% rate noted above is not likely to be representative of the entire cohort's experience.

Table 21 shows all adverse events considered by site investigators to be possibly or probably related to the procedure. Overall, twenty events were probably related to the procedure. **Table 22** provides more detail on these subjects.

TABLE 21
Frequency of Adverse Events and Relationship to Procedure

Event Category	Severity of Event	Relation to Procedure		Total
		Possibly related	Probably related	
Arrhythmias, possibly requiring drugs and/or DC cardioversion	Mild	1	-	1
	Moderate	3	-	3
	Severe	1	1	2
Bleeding	Mild	1	1	2
	Moderate	1	-	1
Cardiac perforation and/or resulting hemopericardium and/or tamponade	Severe	-	1	1
Drug reactions	Moderate	1	1	2
Femoral arteriovenous fistula	Moderate	-	1	1
Infection	Moderate	1	-	1
Other	Mild	8	14	22
	Moderate	9	2	11
	Severe	-	2	2
SA block possibly requiring a permanent pacemaker	Moderate	-	1	1
Total		26	24	50

TABLE 22
Frequency of Adverse Events Judged to be Probably Related to Procedure

Description	Frequency
Skin irritation	5
Sore throat	4
Pericarditis*	2
Sinus pause*	2
Back pain	2
Tamponade*	1
Nausea	1
Deep vein thrombosis	1
Femoral AV fistula*	1
Arrhythmia**	1
Swelling of lip	1
Weakness	1
Bleeding	1
SA node damage*	1
Total	**24**

*Previously described
**Hospitalization one month after linear ablation for elective cardioversion that was canceled due to spontaneous reversion to NSR

Table 23 provides information about four adverse events reported by investigators to be possibly or probably related to the study device.

TABLE 23
Frequency of Adverse Events and Relationship to Device

Category	Severity of Event	Relation to Device		Total
		Possibly related	Probably related	
Drug reactions	Moderate	1	-	1
Other	Mild	4	-	4
SA block possibly requiring a permanent pacemaker	Moderate	-	1	1
Total		5	1	6

*previously described

The five "possibly" device-related events in Phase III were as follows:

- Subject III-606. Subject described previously with post-procedure pericarditis and pneumonia.

- Subject III-603. Subject with undiagnosed inspiratory chest pain, treated with ibuprofen. No evidence of pulmonary embolism or pericarditis.

- Subject III-509. Subject hospitalized one month after linear ablation for recurrent AF. A low INR measurement was observed, which was attributed to a drug reaction (sotalol). It is unclear why this adverse event was judged to be possibly related to the device.

- Subject III-607. Subject hospitalized 111 days after linear ablation for AV node ablation plus pacemaker placement. This ablation was aborted and reattempted successfully two weeks later. It is unclear why this was reported as an AE related to the study device.

The REVELATION® Tx Microcatheter Ablation System ablation procedure has a very strong safety profile of a 4.2% (4/95 procedures) rate of "major complications," with no phrenic nerve injuries and 1% (1/95 procedures) rate of acute sinus node injury.

7.6.2 Secondary Endpoint

Quality of life scores at six months after linear RF ablation comprised the secondary outcome in the REVELATION® Tx Microcatheter Ablation System clinical investigations. Changes in SF-36 and AFSS scores, as well as changes in symptoms typically associated with AF episodes, are reported below.

Short Form-36

Changes in SF-36 scores suggested marked improvements in quality of life after treatment of symptomatic paroxysmal AF with linear ablation using the REVELATION® Tx Microcatheter Ablation System (**Table 24**). Statistically significant improvements occurred in all but one ("general health") SF-36 dimension. The percentage of subjects who reported a clinically significant (> 10 points) improvement was between 30 and 55% for each dimension (**Table 25**), indicating a clinically important improvement in quality of life associated with the RF ablation procedure. Improvements were largest in vitality, social functioning, and bodily pain. Additionally, for these three scales and role emotional, the mean scores were improved from substantially below the U.S. norms at baseline to the level of the US norms six months after ablation. Mean changes were clinically significant (>10 points) in four of the eight categories.

TABLE 24
Baseline and 6-Month SF-36 Scores Among 6-Month Completers

SF-36 Scale	General US Population Scores[1]		Baseline (n = 81 – 83[2])		Six Month (n=78 - 80)	
	Mean	SD	Mean	SE	Mean	SE
Physical Functioning	84.2	23.3	71.1	25.8	77.2[a]	25.2
Role Physical	80.9	34.0	42.1	43.5	59.4[b]	44.0
Role Emotional	81.3	33.0	66.7	39.5	81.0[c]	36.1
Bodily Pain	75.2	23.7	70.7	24.1	79.7[b]	22.3
General Health	71.9	20.3	63.0	21.2	63.4	20.5
Vitality	60.9	20.9	47.3	22.3	58.7[d]	20.9
Social Functioning	83.3	22.7	71.1	26.5	83.0[d]	21.4
Mental Health	74.7	18.1	74.9	16.0	78.9[e]	15.5

a: p = 0.026; b: p = 0.002; c: p = 0.006; d: p <.0001; e: p = 0.032 by paired t-test.
1: The general population was sampled to acquire normative values for these domains (n=6,742)
2: Range of sample size at baseline and 6 months follow-up

TABLE 25
Clinically Significant (>10 points) Improvements in SF-36 Scores (N=84) Six Months After Ablation

SF-36 Dimension	Frequency	%
Physical Functioning	28	33.3
Role Physical	31	36.9
Role Emotional	27	32.1
Bodily Pain	39	46.4
General Health	26	31.0
Vitality	46	54.8
Social Functioning	43	51.2
Mental Health	25	29.8

Atrial Fibrillation Severity Scale

The AFSS was employed to quantify subjects' perceptions of the quality of life burden due to symptomatic AF. At 6 months, AFSS scores showed substantial and significant improvements in episode frequency, duration and severity (**Table 26**). Fifty percent of subjects achieved an improvement of 10 or more points in reported

episode frequency (**Table 27**). The main stated goal of linear RF ablation for AF was to reduce symptomatic AF episode frequency. However, the mechanism of action of RF ablation in AF may also reduce episode duration and severity. As shown in **Table 27,** subjects who underwent RF ablation with REVELATION® Tx Microcatheter Ablation System also showed clinically important reductions in episode duration (35%) and severity (49%).

TABLE 26
Baseline and Six Month AFSS and Component Scores

Score	Baseline (N=82 - 83)		Six Month (N=68 – 70*)	
	Mean	SE	Mean	SE
Episode Frequency	33.6	2.1	51.4[a]	2.9
Episode Duration	44.1	2.9	60.0[b]	3.9
Episode Severity	49.4	2.6	66.7[a]	3.1
Total AFSS	41.9	1.6	58.7[a]	2.5

a: p <.0001; b: p = 0.001; by paired t test
* Subjects who do not experience AF at follow-up did not answer some questions as they were not applicable.

TABLE 27
Clinical Improvement (Increase > 10 points) in Six-month AFSS Scores (N=84)

AFSS Domain	Frequency	%
Episode Frequency	42	50.0
Episode Duration	29	34.5
Episode Severity	41	48.8
AFSS Total	37	44.0

Table 28 shows the relationship between the baseline number of symptomatic AF episodes recorded by event monitors and the frequency, duration and severity questions of the AFSS instrument. Baseline episode frequency was associated with AFSS frequency but not with duration or severity. **Table 29** shows the relationship between the change in symptomatic AF episode counts from baseline to six months (i.e., the primary success outcome) and the change in the frequency, duration and severity subscales of the AFSS. Subjects who met the target-level reduction in AF episode counts recorded by event monitors also reported large increases in the AFSS frequency subscale. Additionally, subjects who reported target-level decreases in symptomatic AF episode counts also reported improvements in duration and severity of episodes.

TABLE 28
Relationship Between Baseline Number of Symptomatic AF Episodes and AFSS Frequency, Duration, and Severity Subscales (N=84)

Baseline Symptomatic AF Episodes	Frequency		Duration		Severity		Frequency
	Mean	SE	Mean	SE	Mean	SE	
3 to 4	44.3	3.6	49.5	5.0	46.8	4.5	29
5 to 9	33.5	3.1	38.6	4.3	52.0	3.2	31
10 to 14	25.6	2.9	46.0	9.8	55.6	7.9	9
15 to 19	20.0	6.2	32.7	9.2	30.2	8.6	7
More than 20	17.5	4.5	53.6	12.3	58.3	13.1	8

TABLE 29
Change in Symptomatic AF Episode Frequency and Change in AFSS Frequency, Duration, and Severity Subscales (N=77)

Target-level Reduction in Symptomatic AF Episodes	Frequency		Duration		Severity		Frequency
	Mean	SE	Mean	SE	Mean	SE	
No	5.6	3.1	3.7	6.2	7.4	4.3	30
Yes	28.6	4.9	23.0	5.2	21.1	5.2	47

7.7 Additional Results

7.7.1 Symptoms Associated with AF Episodes

Symptoms typically associated with AF episodes decreased markedly and statistically significantly at three and six months after ablation compared to baseline (**Table 30**). At the six month visit, palpitations were reduced by 53%, chest pain by 65%, shortness of breath by 45%, lightheadedness by 62% and fatigue/weakness by 54%. These findings corroborate episode reductions and quality of life changes described above.

TABLE 30
Symptoms Associated with AF Episodes by Study Visit

Symptom	Study Visit						
	Baseline (N=83)		3 Months (N=77)		6 Months (N=79)		
	Freq.	%	Freq.	%	Freq.	%	% reduction*
Palpitations	72	86.7	42	54.5[a]	32	40.5[a]	53.3
Chest pain	18	21.7	6	7.8[b]	6	7.6[b]	65.0
Shortness of breath	40	48.2	19	24.7[c]	21	26.6[f]	44.8
Lightheadedness	28	33.7	13	16.9[d]	10	12.7[g]	62.3
Fatigue/ Weakness	46	55.4	20	26.0[e]	20	25.3[e]	54.3

a) $p < 0.0001$; b) $p = 0.008$; c) $p = 0.0007$; d) $p = 0.02$; e) $p = 0.0002$; f) $p = 0.0002$; g) $p = 0.003$, all by McNemar's test.
*percent reduction from baseline

Both the primary and secondary outcomes in the REVELATION® Tx Microcatheter Ablation System clinical investigations were based on symptoms of AF. Consistent with the marked reduction in the presence of common symptoms of AF at six months, all secondary quality of life outcomes showed large and statistically significant improvements in various domains of overall health as well as specific quality of life measures related to symptomatic AF. AF-related quality of life assessments were associated well with the primary outcome measured in the trial (AF episodes recorded by event monitors); and the change in AF-specific quality of life measurements was also directly related to the change in episode counts, supporting the internal and external validity of the quality of life measurements performed in this trial. Taken together, these results provide substantial evidence of an important clinical benefit for subjects undergoing treatment of symptomatic, paroxysmal AF with the REVELATION® Tx Microcatheter Ablation System.

7.7.2 EKG Findings in Follow-up

Electrocardiograms were performed and read by study investigators at baseline, discharge and at one, three and six months of follow-up. **Table 31** shows EKG findings at baseline and follow-up study visits. Normal sinus rhythm and sinus bradycardia were present in 48.8% and 15.1% of patients respectively at 6 months, for a total of 63.9% of patients. AF was present in 25% of subjects at baseline and in 21% at six months of follow-up.

TABLE 31
EKG Findings at Baseline and Follow-Up

Rhythm	Study Visit									
	Baseline N=93		Discharge N=92		Month 1 N=90		Month 3 N=87		Month 6 N=86	
	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%
NSR	40	43.0	57	62.0	48	53.3	41	47.1	42	48.8
Sinus bradycardia	23	24.7	18	19.6	20	22.2	20	23.0	13	15.1
Premature atrial contractions	3	3.2	5	5.4	5	5.6	4	4.6	1	1.2
Atrial fibrillation	23	24.7	8	8.7	17	18.9	15	17.2	18	20.9
Atrial flutter	3	3.2	1	1.1	2	2.2	2	2.3	6	7.0
Unifocal PVCs	3	3.2	2	2.2	-	-	-	-	2	2.3
Paced	5	5.4	8	8.7	4	4.4	12	13.8	14	16.3

7.7.3 NYHA Status

There was relatively little change in NYHA class from baseline in these subjects, as illustrated in **Table 32**. There was an increase in the percentage of subjects in Class I from baseline (77.4%) to six months (85.9), but two subjects were noted to be NYHA Class III at six months whereas none was at the level at baseline. One of those subjects (1611) entered the study with congestive heart failure that continued to worsen and the other (1408) subject is an insulin dependent diabetic with fluid volume overload in response to Diovan therapy.

TABLE 32
NYHA Class

Class	Definition	Pre-Ablation		3 Months Post-Ablation		6 Months Post-Ablation	
		Freq.	%	Freq.	%	Freq.	%
I	No limitations of activities; no symptoms from ordinary activity.	72	77.4	67	80.7	67	85.9
II	Slight limitation of activity; comfortable at rest or with slight exertion.	21	22.6	14	16.9	9	11.5
III	Marked limitation of activity; comfortable only at rest.	0	0	2	2.4	2	2.6
IV	Confined to a bed or chair; any physical activity brings on discomfort, and symptoms also occur at rest.	0	0	0	0	0	0
Total		90[a]	100.0	83	100.0	78	100.0

a) NYHA status not available for 2 subjects

7.7.4 Hospitalizations and Emergency Room Visits

There were only 6 reports (6 subjects) of emergency room visits for atrial fibrillation among these study subjects over the 24 months of follow up, and a total of 13 hospitalizations (11 subjects, **Table 33**)

TABLE 33
Hospitalization and Emergency Room Visits

Type of Visit	Month of Follow-Up Visit				
	1	3	6	12	24
Emergency Room	1	1	3	0	1
Hospitalization	1	4	5	2	1
Subjects per visit	89	83	79	40	29

8.0 RISK/BENEFIT ANALYSIS

8.1 Benefits

AF is the most prevalent arrhythmia and is associated with various risks if left unattended. Patients often experience palpitations, shortness of breath and fatigue. These changes in clinical condition, along with the side effects associated with various medications used to treat AF, have a substantial, negative impact the patient's overall quality of life. This non-randomized, single-arm clinical trial has provided sufficient evidence to show that treatment of AF patients through linear radiofrequency ablation of the right atrium, using the REVELATION® Tx Microcatheter Ablation System, is both safe and effective. Effectiveness was shown by demonstrating that subjects treated with the REVELATION® Tx exhibited clinically important reductions in the frequency of patient reported symptomatic AF while evidencing an excellent safety profile, thus achieving the study's primary endpoint. These beneficial results were accentuated by improved quality of life as measured by both the SF-36 scoring system and the AFSS. More than one half of study patients exhibited targeted levels of decreases in symptomatic AF, thus achieving the primary endpoint.

The REVELATION® Tx Microcatheter Ablation System exhibited an excellent safety profile. No cases of stroke or pulmonary vein stenosis occurred with the use of the REVELATION® Tx Microcatheter Ablation System during the course of the trial. The primary endpoint was supported by decrease in patient reported episodes of symptomatic AF and increased quality of life endpoints showing that the REVELATION® Tx Microcatheter Ablation System was associated with decreased episodes of symptomatic AF. Secondary endpoint success criteria were significantly improved for SF-36 and AFSS.

Weighing in favor of the benefits of the REVELATION® Tx Microcatheter Ablation System is the lack of minimally invasive treatment options with the same level of safety associated with the REVELATION® Tx Microcatheter Ablation System. Other than invasive treatments (left atrial ablation, Cox-Maze procedure), currently, additional treatment options are not available to those patients suffering from drug refractory symptomatic AF. The use of the REVELATION® Tx may provide the following benefits:

- Offers a safe treatment of symptomatic AF in patients who are refractory to AADs.
- Restoration of normal sinus rhythm and effective mechanical AV synchrony.
- Reduction of the risk of thromboembolism from the left atrium.
- Reduction in patient discomfort due to palpitations.
- Modification of the characteristics of the arrhythmia and/or its clinical manifestations (e.g., fewer clinical events are noted during follow-up).

- Offers a technique to treat AF without undergoing more complex and risky surgical procedures (e.g., compartment or maze procedures).

8.2 Risks

Any cardiac ablation device carries risk. Risks to subjects enrolled in this study include all those risks currently associated with all electrophysiology diagnostic procedures and radiofrequency catheter ablation procedures. The risks of the procedure are related primarily to mechanical injury to the heart and vessels from catheter manipulation and thermal injury due to RF current delivery, including the risk of thromboembolism and myocardial infarction. The standard risks of anesthesia also exist and include allergic reactions, medical complications and death. Risks of the procedure, not events necessarily seen during the clinical study, are characterized by category as follows:

- Major Complications (may be considered either device or procedure-related):
  - Arterial embolization
  - Arrhythmias, possibly requiring drugs and/or DC cardioversion
  - Atrioventricular block or nodal dysfunction possibly requiring a permanent pacemaker
  - Cardiac perforation and/or resulting hemopericardium and/or tamponade
  - Death
  - Emergent thoracotomy
  - Endocarditis
  - Myocardial infarction
  - Nerve damage
  - Pneumothorax
  - Sino-atrial block: sinus pauses requiring a permanent pacemaker
  - Stroke
  - Thromboembolism/pulmonary embolism
  - Valve or cardiac structure damage

- Minor Complications (may be considered either device or procedure related):
  - Bleeding
  - Femoral arteriovenous fistula (if event results in an extended hospital stay, adverse event was to be categorized as a serious adverse event)
  - Femoral artery injury
  - Infection
  - Pericardial effusion

- Other Complications (not considered device or procedure-related):
  - Drug reactions

In addition to the above mentioned risks, Cardima has also noted potential mechanical and/or electrical failure modes. However, based upon extensive testing

conducted to characterize the forces necessary to induce mechanical and electrical failures, Cardima has found that the REVELATION® Tx Microcatheter Ablation System can be safely used without failure under the conditions for which it is intended. To assure the minimization and mitigation of the before mentioned potential risks, appropriate biocompatibility testing has been conducted on the REVELATION® Tx Microcatheter Ablation System, and has demonstrated the device materials to be safe, suitable and biocompatible for its intended use. In addition, a failure modes and effects analysis has been conducted on the device to characterize product performance, safety margins, and failure modes. Results from this analysis have been used to set appropriate performance specifications for the REVELATION® Tx Microcatheter Ablation System, and to assure the consistency and quality of the device.

Nonetheless, the following points were demonstrated in the clinical study:

- No deaths were associated with use of the REVELATION® Tx Microcatheter Ablation System for right atrial ablation.

- Four serious adverse events were noted in three subjects during the first week after catheter ablation (cardiac tamponade; SA block requiring a permanent pacemaker; pneumonia; and femoral arteriovenous fistula). Only one of these devices was associated with the use of the REVELATION® Tx Microcatheter Ablation System. All four of the serious adverse events were determined as "probably" having been related to the procedure.

- Three serious adverse events, more than one week post-procedure, occurred in Phase III subjects. None of these events were related to the procedure or the device. Two of the events were related specifically to pacemaker problems. It is uncertain why the third occurrence (elective hospitalization for pulmonary vein ablation) was categorized as a serious adverse event.

- Of the 93 subjects in Phase III, 22 experienced a total of 50 adverse events, possibly or probably related to the device and/or the procedure.

- One subject experienced SA block that required implantation of a permanent pacemaker. This event was considered probably related to the device.

9.0 CONCLUSIONS

Atrial fibrillation refractory to antiarrhythmic drugs is a common and important clinical problem. Approved treatment options for patients with drug-refractory AF are currently very limited.

The Cardima REVELATION® Tx Microcatheter Ablation System was designed to mimic the lesions created during the surgical "maze" procedure developed by Dr. James Cox in the late 1980s.[26] In the maze procedure, the atrium is incised and sewn in several strategic locations during open-heart surgery. The maze procedure has been shown to be very effective for the treatment of highly symptomatic paroxysmal AF, with 5-year success rates reported to be greater than 95%.[27] The Cox-Maze procedure includes lesions in both the left and right atria. Because it requires open surgery, the Cox-Maze procedure is performed only very rarely.

The REVELATION® Tx Microcatheter Ablation System was designed to create maze-like lesions by an endovascular route and using RF energy instead of a surgical scalpel. The Cardima pivotal trial described herein (Phase III, IDE G970280/S39) showed that RF ablation in the right atrium using the REVELATION® Tx Microcatheter Ablation System can safely produce right atrial ablation lesions that result in a documented reduction of both episode frequency and the severity of symptoms of paroxysmal AF.

Several aspects of the trial are highlighted:

- The trial was designed in accordance with the recommendations of an FDA Circulatory System Devices Panel Meeting (July 22, 1998). The Panel recommended a single-arm, non-randomized trial design with subjects as their own control and follow-up to 6 months.
- The Panel recommended that success be considered a 50 – 75% reduction in the frequency of symptomatic AF episodes from baseline.
- The Panel noted that improved quality of life may be a "very important outcome."
- The trial showed that 58% of treated subjects achieved episode reduction consistent with the above definition of success.
- The trial showed concomitant improvements in quality of life as measured by 2 accepted QOL instruments.
- The trial showed that the safety profile of RF ablation using the REVELATION® Tx Microcatheter Ablation System is very acceptable. Importantly, no patient in the Phase III study experienced stroke, death or atrioesophageal fistula.

Right atrial ablation for AF has been documented in several studies to have a clinically important success rate (**Table 33**). In these studies, single-tip catheters (or, in one case, a multielectrode catheter) were used to create right atrial lesions similar to those performed in the REVELATION® Tx Microcatheter Ablation System study.

The effectiveness observed in these studies provides strong prior background support for the effectiveness observed in the pivotal trial described herein.

TABLE 33
Studies of Right Atrial Ablation for Atrial Fibrillation

Author	Intervention	Success Rate
Montenero, 2004	Lateral/septal/isthmus (ILR)	80%
Kocheril, 2001	Superior/septal/anterior/isthmus	79%
Gasparini, 2000	Posterior/isthmus	75%
Garg, 1999	Posterior/septal/anterior/isthmus	67%
Calo, 2004	Lateral/septal/CS/isthmus	66%
Natale, 1999	2 to 4 lesions in RA	61%
Gaita, 1998	Horizontal lateral/septal/isthmus	56%
Montenero, 2002	Lateral/septal/isthmus	55%
Haissaguerre, 1996	RA ablation	53%
Pappone, 1999	Posterior/septal/medial/isthmus	50%
Calkins, 1999	NS (multielectrode, HRT)	20%

Left atrial catheter ablation (LACA) is commonly performed in the US, with ablation performed either in the pulmonary veins or in the left atrium itself. Several randomized studies of LACA have shown it to be an effective treatment compared to continued medical management.[28,29,30,31] However, the left atrial approach has several disadvantages. First, it requires a transseptal puncture, which may cause permanent injury in the heart. Second, ablation in the left atrium may cause thrombus to adhere to the ablation catheter; if the thrombus embolizes, the patient may experience stroke. Studies have shown that stroke occurs at an unacceptably high rate during LACA. Finally, atrioesophageal fistula is a known and often fatal adverse event occurring during LACA. Atrioesophageal fistula occurs when an ablation lesion in the posterior portion of the left atrium becomes necrotic and eventually communicates with the esophagus. Such fistulae may occur up to 2 weeks after the procedure. Because of the configuration of the REVELATION® Tx Microcatheter, and because it is used only in the right atrium, the risk of atrioesophageal fistula with REVELATION® Tx Microcatheter treatment is extremely low.

Several advantages of right atrial ablation with the REVELATION® Tx Microcatheter are apparent:

- The catheter is easily delivered into the right atrium.
- Placement of the catheter against the right atrial wall is simple.
- Without catheter movement, a continuous lesion can be created in the right atrium by serial firing of the device's electrodes.

- Precise temperature feedback prevents over-ablation.
- No transseptal puncture is required.
- The risk of atrioesophageal fistula is low.
- The risk of device-related stroke is low (providing that the foramen ovale is not patent).

The data and information submitted in support of the Cardima REVELATION® Tx Microcatheter Ablation System comprise valid scientific evidence for the proposed indications for use. Catheter-based right atrial RF ablation using a linear catheter represents a clinically valid and safe approach to symptomatic paroxysmal AF. The Cardima REVELATION® Tx Microcatheter Ablation System will serve as a valuable clinical tool to further increase options for patients who are refractory to antiarrhythmic drugs and for whom the Cox-Maze procedure is not an option.

Finally, right atrial ablation is recently becoming more recognized as an important adjunct to catheter ablation strategies for AF. Biatrial mapping studies have shown that triggers of AF occur in both the left and right atria. Prominent developers of AF ablation strategies in Bordeaux, France have written regarding chronic AF ablation:

> "There is a ceiling of ablation within the LA beyond which further ablation is unlikely to result in a clinical benefit and should prompt evaluation of the contribution of the right atrium to maintenance of AF. The stepwise approach benefits from the integration of anatomic and electrophysiologic information to achieve a high level of success in termination of chronic AF by catheter ablation."[32]

Cardima believes the right atrium plays an important role in paroxysmal AF as well as chronic AF, and ablation of the right atrium is likely to contribute to overall patient success in AF.[33,34,35]

Left atrial catheter ablation is in very common use today in the US. However, no catheters are approved for such ablation. As a result, practices vary widely and the safety profile of LACA is in question. Further, many practitioners avoid LACA due to its risk and are left without a viable treatment option for patients with drug-refractory AF. Ablation of the right atrium with the REVELATION® Tx Microcatheter Ablation System represents a mechanism by which catheter ablation can be provided to patients safely and under more regulatory scrutiny.

REFERENCES

1. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. 1995. Prevalence, age distribution and gender of subjects with atrial fibrillation: analysis and implications. *Archives of Internal Medicine* 155:469-473.
2. Anonymous. 1990. Preliminary report of the Stroke Prevention in Atrial Fibrillation study. *New England Journal of Medicine* 322:863-868.
3. Friberg J, Buch P, Scharling H, Gadsbphioll N, Jensen GB. 2003. Rising rates of hospital admissions for atrial fibrillation. *Epidemiology* 14:666–672.
4. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. 2001. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *Journal of the American Medical Association* 285:2370-2375.
5. Chug S, Blackshear J, Shen WK, Hammill S, Gersh B. 2001. Epidemiology and natural history of atrial fibrillation: clinical implications. *Journal of the American College of Cardiology* 37:371-378.
6. Stewart S, Hart CL, Hole DJ, McMurray JJ. 2002. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *American Journal of Medicine* 113:359-364.
7. Wolf PA, Abbott RD, Kannel WB. 1991. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 22:983-988.
8. van den Berg MP, Hassink RJ, Tuinenburg AE, van Sonderen EF, Lefrandt JD, de Kam PJ, van Gelder IC, Smit AJ, Sanderman R, Crijns HJ. 2001. Quality of life in subjects with paroxysmal atrial fibrillation and its predictors: importance of the autonomic nervous system. *European Heart Journal* 22:247-253.
9. Reynolds MR, Lavelle T, Essebag V, Cohen DJ, Zimetbaum P. 2006. Influence of age, sex, and atrial fibrillation recurrence on quality of life outcomes in a population of patients with new-onset atrial fibrillation: the Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) study. *American Heart Journal*:152: 1097-103.
10. Saksena S, Madan, N. 2003. Hybrid therapy of atrial fibrillation: algorithms and outcome. *Journal of Interventional Cardiac Electrophysiology* 9: 235-247.
11. Jais P. Haissaguerre M, Shah DC, Chouairi S, Gencel L, Hocini M, Clementy J. 1997. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. *Circulation* 95:572-576.
12. Kerr C, Humphries K, Talajic M, Klien G, Connolly S, Green M, Boone J, Sheldon R, Dorian P, Newman D. 2005. Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: Results from the Canadian Registry of Atrial Fibrillation. *American Heart Journal* 149:489-496.
13. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN,

Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. 2006. ACC/AHA/ESC 2006 guidelines for the management of subjects with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology. *Circulation*:114:257-354.

14. Cox JL, Schuessler RB, Lappas DG, Boineau JP. An 8 ½ year clinical experience with surgery for atrial fibrillation. *Annals of Surgery* 224:267-275.
15. Arentz T, Jander N, von Rosenthal J, Blum T, Furmaier R, Gornandt L, Josef Neumann F, Kalusche D. 2003. Incidence of pulmonary vein stenosis 2 years after radiofrequency catheter ablation of refractory atrial fibrillation. *European Heart Journal* 24: 963-969.
16. Iesaka Y. 2006. Complications of catheter ablation of atrial fibrillation: cause, prevention, and management. *Journal of Cardiovascular Electrophysiology* 17: S50-S55.
17. Gerstenfeld E, Guerra P, Sparks P, Hattori K, Lesh, M. 2001. Clinical outcome after radiofrequency catheter ablation of focal atrial fibrillation triggers. *Journal of Cardiovascular Electrophysiology* 12:900-908.
18. Cheema A, Vasamreddy CR, Dalal D, Marine JE, Dong J, Henrikson CA, Spragg D, Cheng A, Nazarian S, Sinha S, Halperin H, Berger R, Calkins H. 2006. Long-term single procedure efficacy of catheter ablation of atrial fibrillation. *Journal of Interventional Cardiac Electrophysiology* 15:145-155.
19. Saksena S, Prakash A, Krol R, Shankar A. 1999. Regional endocardial mapping of spontaneous and induced atrial fibrillation in subjects with heart disease and refractory atrial fibrillation. *American Journal of Cardiology* 84:880-889.
20. McGavin A, Kalman J. 2006. Atrial anatomy and imaging in atrial fibrillation ablation. *Journal of Cardiovascular Electrophysiology* 17: S8-15.
21. Chen PS, Chou CC, Tan AY, Zhou S, Fishbein M, Hwang C, Karagueuzian H, Lin SF. 2006. The mechanisms of atrial fibrillation. *Journal of Cardiovascular Electrophysiology* 17:S2-S7.
22. Jumrussirikul P, Atiga WL, Lardo AC, Berger RD, Halperin H, Hutchins GM, Calkins H. 2000. Prospective comparison of lesions created using a multipolar microcathether ablation system with those created using a pullback approach with standard radiofrequency ablation in the canine atrium. *Pacing and Clinical Electrophysiology: PACE* 23:203-213.
23. Recommended Clinical Study Design for Ventricular Tachycardia – Guidance for Industry and for FDA Reviewers. US Department of Health and Human Services,

Food and Drug Administration, Center for Devices and Radiological Health, May 7, 1999.
24. http://ftp.sas.com/techsup/download/stat/glmm800.html
25. Dorian, P. (Toronto, Ontario, 1999)
26. Cox J, Schuessler R, D'Agostino H, Stone C, Chang B, Cain M, Corr P, Boineau J. 1991. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. *Journal of Thoracic and Cardiovascular Surgery* 101: 569-583.
27. Prasad S, Maniar H, Camillo C, Schuessler R, Boineau J, Sundt T, Cox J, Damiano R. 2003. The Cox maze III procedure for atrial fibrillation: long-term efficacy in patients undergoing lone versus concomitant procedures. *Journal of Thoracic and Cardiovascular Surgery* 126: 1822-1828.
28. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F, Bates ER, Lehmann MH, Vicedomini G, Augello G, Agricola E, Sala S, Vicenzo S, Morady F. 2006. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *New England Journal of Medicine* 354:934-941.
29. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, Santagostino A, LiVolsi L, Pappone N, Radinovic A, Manguso F, Santinelli V. 2006. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. *Journal of the American College of Cardiology* 48:2340-2347.
30. Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, Turco P, Pascotto P, Fazzari M, Vitale DF. 2006. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). *European Heart Journal* 27:216-221.
31. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A. 2006. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *Journal of the American Medical Association* 293:2634-2640.
32. O'Neill MD, Jais P, Takahasi Y, Jonsson A, Sacher F, Hocini M, Sanders P, Rostock T, Rotter M, Pernat A, Clementy J, Haissaguerre M. 2006. The stepwise ablation approach for chronic atrial fibrillation – Evidence for a cumulative effect. *Journal of Interventional Cardiac Electrophysiology* 16:153-167.
33. Calo L, Lamberti F, Loricchio ML, Castro A, Shpun S, Boggi A, Pandozi C, Santini M. 2004. Long-term follow-up of right atrial ablation in patients with atrial fibrillation: efficacy and impact of a hybrid approach on quality of life. *Journal of Cardiovascular Electrophysiology* 15:37-43.
34. Calo L, Lamberti F, Loricchio ML, De Ruvo E, Colivicchi F, Bianconi L, Pandozi C, Santini M. 2006. Left atrial ablation versus biatrial ablation for persistent and

permanent atrial fibrillation: a prospective and randomized study. *Journal of the American College of Cardiology* 47:2504-2512.

35. Gasparini M, Coltorti F, Mantica M, Galimberti P, Ceriotti C, Beatty G. 2000. Noncontact system-guided simplified right atrial linear lesions using radiofrequency transcatheter ablation for treatment of refractory atrial fibrillation. *Pacing and Clinical Electrophysiology: PACE* 23:1843-1847.