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

EXECUTIVE SUMMARY

PUBLIC HEALTH NEED

- It is estimated that over 2 million people in the United States (US) suffer from paroxysmal atrial fibrillation (AF).

- AF is the most common rhythm disorder among US patients hospitalized with a primary diagnosis of arrhythmia.

- Patients with paroxysmal AF are often highly symptomatic, especially in the areas of physical role function, emotional role function, vitality and general health.[1]

- The standard treatment for paroxysmal AF is pharmacotherapy, consisting of antiarrhythmic drugs (AADs) to keep patients in normal sinus rhythm. Use of AADs is often limited because of challenging side-effect profiles. Moreover, patients commonly become refractory to AADs.

- The "gold-standard" surgical treatment for atrial fibrillation is the Cox-Maze Procedure. The Cox-Maze procedure is highly effective, but, as an open heart procedure, is only performed on patients having another cardiac surgical procedure such as valve replacement. The Maze procedure creates lines of electrical block in both the right and left atria via incisions or ablation.

- Catheter ablation is considered a second-line treatment of AF. Prior to the REVELATION® Tx Microcatheter Ablation System study, right-sided catheter ablation studies have been published with highly variable results. However to date, all procedures have been done with hot-tip catheters using a "drag and burn" technique.

- 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. Additionally, left-sided catheter ablation procedures are complex to perform and have a high rate of adverse events. Serious adverse events from left-atrium catheter ablation include stroke, esophageal fistula, cerebral air embolism, and death.[2,3]

- After years of experience, it is now recognized that left-sided catheter ablation does not reliably cure AF[4] and right-atrium ablation is increasingly utilized as

a concomitant procedure with left-atrial ablation for paroxysmal AF, consistent with the Cox-Maze surgical approach.

- Consistent with the Cox-Maze surgical approach, it has been shown that the addition of right-atrium lesions, similar to those created in the Cardima trials, improved effectiveness outcomes of left-sided catheter ablation in patients with persistent or permanent AF.[5]

- Catheter ablation in the right atrium alone has been shown to be effective for the treatment of paroxysmal AF.[6,7,8, 9]

- The REVELATION® Tx Microcatheter Ablation System was designed to mimic the lesions created in the right atrium during the Cox-Maze procedure for symptomatic patients who are refractory to AADs and for whom the Cox-Maze procedure is not an option.

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]

DEVICE DESCRIPTION

- The REVELATION® Tx Microcatheter Ablation System consists 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 Microcatheter Ablation System include Cardima's guiding catheter, NAVIPORT (cleared under K974683), the Tx SELECT Switchbox and the associated connecting cables. The connecting cables and the passive switchbox (Tx SELECT Switchbox) are the interface between the ablation catheter and any commercially available electrocardiograph, pacing stimulator and any commercially available endocardial radiofrequency (RF) generator that is thermocouple-compatible.

[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."

- A part of the system, the NAVABLATOR® catheter, was optionally available for ablation of the isthmus.[b]

- 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 Microcatheter was designed for the creation of thin continuous lesions in the atrium for the treatment of AF by placing the linear array of electrodes along a desired trajectory in the atrium, conforming to the curvature of the wall.

RELEVANT REGULATORY BACKGROUND

- FDA approved a feasibility study (Phase IIa) of 10 patients in December 1997.

- On July 22, 1998, the Circulatory System Devices (CSD) Advisory Committee met to discuss the design of clinical studies for atrial fibrillation. Among other recommendations, the Panel concluded that clinical trials for atrial fibrillation devices should be single arm studies using patients as their own controls. The Panel specifically recommended a population that failed at least two AADs or amiodarone and at baseline should have at least two episodes of symptomatic AF over a three month period prior to study entry. Subsequently, the CSD Panel met in April 2000 and re-affirmed these recommendations. The Cardima pivotal trial design adopted all of the recommendations of the CSD Advisory Committee for the design of a study to examine the safety and effectiveness of a device for treatment of atrial fibrillation.

- Cardima initiated, in March 1999, the Phase IIb, prospective multi-center, clinical study to evaluate the safety and effectiveness of the REVELATION® Tx Microcatheter Ablation System for treating drug refractory patients with symptomatic atrial fibrillation at 9 centers, enrolling 38 patients.

- In April 2000, FDA approved the protocol for expansion of this study as a Phase III trial with a sample size of 80 patients. The protocol was virtually identical to the Phase IIb protocol, except that in addition to other catheters for

[b] Please see footnote “d” on page 6 for a protocol excerpt describing the role of the NAVABALTOR® during the clinical trial.

isthmus ablation, it included the optional NAVABLATOR® catheter for isthmus ablation.

- The PMA Clinical Module was submitted in September 2002 with 38 patients from Phase IIb and 61 subjects from Phase III.

- The Circulatory System Devices Advisory Committee convened on May 29, 2003 and reviewed only Phase IIb data and 61 subjects from Phase III who had completed 6 months of follow-up. The CSD Advisory Committee did not have access to the complete pivotal trial data, which was submitted in an amended PMA by Cardima to FDA that included the completed Phase III clinical data and additional data analysis.

PRECLINICAL STUDIES

- Four proof of concept studies performed in two animal models consistently demonstrated that the device met the design and performance criteria as a diagnostic and ablation catheter.

    - In a goat model, assessment of device performance, lesion formation, and depth of ablation, demonstrated that continuous transmural lesions were obtained, there was no coagulum on electrodes, and a large increase in pacing threshold after ablation.

    - In a canine model, at a predetermined location, there was feasible catheter placement, continuous transmural lesions were obtained, electrograms were of good quality, and minimal coagulum was observed on electrodes.

    - In a canine thigh muscle model, the lesion size and thrombus formation were evaluated. Observations included: continuous lesions formed; thrombus occasionally observed at 50-55ºC; and high blood flow around electrode allowed increased RF power delivery and correlated with deeper and wider RF lesions.

    - A comparison of lesions created with REVELATION® Tx Microcatheter and the standard "drag and burn" approach in a canine model demonstrated that lesions created with REVELATION® Tx Microcatheter were smaller and more likely to be transmural and continuous.[10]

SINGLE CENTER STUDY OF REVELATION® CATHETER

- A single-center clinical study[11] of Cardima's REVELATION® catheter (3.3 F multielectrode catheter) evaluated a continuous right-atrial linear ablation in 29 patients with paroxysmal AF.

- 29 patients with recurrent symptomatic AF refractory to medical therapy underwent linear ablation. Inclusion criteria were symptomatic paroxysmal AF (less than 24 hours in duration) and failure of at least two anti-arrhythmic medications. Post-ablation monitoring, by Holter monitor or event recorder, was pursued when patients reported symptoms.

- Acute procedural success was achieved in 24 patients (83%), where sinus rhythm was restored and AF was not inducible. Long term success was observed in 23 patients (79%) over a mean follow-up of 19.7 months. These patients remained free of symptomatic AF, off of antiarrhythmic medications. There were no complications.

PHASE IIB CLINICAL STUDY OF REVELATION® Tx MICROCATHETER ABLATION SYSTEM

- The Phase IIb clinical study was a prospective, multicenter, single-arm study of 38 subjects with drug-refractory, paroxysmal atrial fibrillation. Subjects underwent right-sided ablation with the REVELATION® Tx Microcatheter and also received an isthmus line ablation with the hot-tip catheter of the investigator's choice (since no atrial flutter ablation catheters were approved at the time.)

- The primary endpoint of the study was a reduction of 50% or greater in the number of symptomatic AF episodes at 6 months compared to baseline. Symptomatic episodes reported by a subject were electrocardiographically confirmed by an independent cardiologist.

- 18 out the 21 (86%) subjects who transmitted rhythm strips met the primary success criteria.

- 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).

PHASE III CLINICAL STUDY OF REVELATION® Tx MICROCATHETER ABALTION SYSTEM

- The Phase III study was a prospective, multicenter single-arm study of 93 patients with drug-refractory atrial fibrillation. The design of the study conformed with the most current guidance of the Circulatory System Devices Panel for devices targeting AF. FDA approved the design of the study, i.e., a single-arm study.

- The primary endpoint of the study was a reduction in the number of documented symptomatic AF episodes at 6 months compared to baseline. Success was defined as a reduction of 50% or more of self-reported symptoms for subjects with 5 or greater episodes at baseline and a 75% or more reduction for subjects with 3 or 4 episodes at baseline.

- An additional clinical success endpoint was a 50 or 75% reduction in symptomatic AF episodes (depending on the baseline burden) while maintained on the same or reduced drug regimen.

- Secondary quality of life endpoints included the Medical Outcomes Study's SF-36 instrument and the Atrial Fibrillation Severity Scale (AFSS).

- Each symptomatic episode recorded by a patient using a handheld cardiac event monitor was electrocardiographically confirmed by an independent cardiologist.

- Subjects were asked to transmit a rhythm strip with the handheld cardiac event monitor on a weekly basis independent of symptoms. 88% of subjects transmitted 3 or more rhythm strips during the 6-month follow-up.

PIVOTAL CLINICAL STUDY RESULTS

- The pivotal trial of the REVELATION® Tx Microcatheter Ablation System met the pre-specified success endpoints. [12]

- As of January 2004, 58% (49 of 84) of subjects met the primary success criteria; 44% (37 of 84) met the additional clinical success endpoint.

- Additionally, and importantly, 35% (30 of 84) of subjects had no episodes at the 6th month endpoint, 79% (67 of 84) had some improvement, and overall there was a 62% mean reduction in episode frequency in the 6th month of follow-up versus baseline.[c]

- The device and procedure had a highly favorable safety profile, especially as compared to left-sided ablation. There were no deaths in the trial. There were 5 serious adverse events in 4 subjects (5.2%); only one of the reported adverse events was determined to be device-related.

NAVABLATOR CATHETER FOR ISTHMUS ABLATION

[c] Numbers exceed 100% because "some improvement" includes complete improvement (no episodes).

- Isthmus ablation with a specific catheter is not important to an evaluation of the REVELATION® Tx Microcatheter Ablation System.

- The use of the NAVABLATOR® for the creation of the isthmus line was always optional, as specified in the protocol. [d]

- When the study was first designed (IIb), there were no catheters approved by FDA for isthmus ablation. The study protocol specified that investigators create the isthmus line with the REVELATION® Tx Microcatheter or an ablation catheter of their preference.

- The NAVABLATOR® was developed as an investigational device, at the request of FDA, to ablate the cavo-tricuspid isthmus in the Phase III trial, since no FDA-approved catheters for atrial flutter ablation were available at that time. Study investigators and FDA felt that isthmus ablation should be included in the protocol as a preventative measure against atrial flutter.

- In the Phase III study, the NAVABLTOR® catheter was optionally available for ablation of the isthmus only after first attempting to create a linear burn with the REVELATION® Tx Microcatheter.

- Only the REVELATION® Tx Microcatheter was used in making linear lesions in the right atrium for the treatment of atrial fibrillation.

- The use of different catheters in ablating the isthmus did not have any effect on the results reported for the primary endpoint of the studies for several reasons. First, a stratified analysis of the results as a function of the catheter used does not alter the outcome notably. Secondly, isthmus ablation was considered effective only for the treatment of atrial flutter. Atrial fibrillation and atrial flutter are distinct disease entities, and isthmus ablation had no clinical role in alleviating or improving the symptoms of atrial fibrillation.

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[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."

- Isthmus ablation with a specific catheter is unimportant because there are now three (3) FDA-approved catheters for the treatment of atrial flutter that could be used on-label with the REVELATION® Tx Microcatheter Ablation System when it is approved.[e]

VALID SCIENTIFIC EVIDENCE IN SUPPORT OF APPROVAL

- FDA regulations provide specific requirements for the scientific evidence to be considered by the Agency in considering the approvability of a PMA (at 21 CFR 860.7(c)(2)). Valid scientific evidence is defined as: evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device.

- The body of evidence provided by Cardima in support of the approvability of the REVELATION® Tx Microcatheter Ablation System conforms with the definition of valid scientific evidence, and the two multi-center studies (IIb, III) fit squarely in the FDA definition of valid scientific evidence.

- The original data submitted in the PMA included:

    - Two well-controlled, multi-center clinical studies, with a total of 131 subjects that demonstrated both safety and effectiveness in reducing the number of symptomatic atrial fibrillation episodes.

- The original data is supplemented by:

    - A single center investigation of the REVELATION® catheter by a qualified expert in 29 patients.

    - Peer-reviewed publications of clinical studies on the effectiveness of the surgical maze procedure, including right-sided procedures;

- The Cardima single arm trials provide valid scientific evidence on which to base a determination of safety and effectiveness. Additionally, any concern regarding the placebo effect is unwarranted since the results are not at all consistent with this explanation for the following reasons:

[e] Irvine Biomedical's Dual 8 Catheter; Biosense Webster's NaviStar ThermoCool Deflectable Diagnostic/Ablation Catheter; Boston Scientific's EPT 1000 XP Catheter.

- The magnitude of the treatment effect required in order for a patient to be counted as a success was high (50% or greater reduction in episodes).

- The primary endpoint was determined 6 months after treatment.

- Self-reported episodes of AF were all confirmed by an independent cardiologist.

- The natural history of paroxysmal AF is well-known; patients do not spontaneously improve. All subjects enrolled in the pivotal trial had a long history of drug refractory AF and were not expected to improve to significant degree with continued medical treatment.

- The treatment effect observed in the Cardima trials are consistent with results reported for the open surgical procedure (Cox-Maze), and other studies of right-side ablation.

- FDA has approved 9 of the10 available ablation catheters on the US market based on single arm studies.[f]

CONCLUSIONS

- The data and information submitted in support of the REVELATION® Tx Microcatheter Ablation System comprise valid scientific evidence, and provide reasonable assurance of safety and effectiveness of the device for the proposed indication for use.

- The Phase IIb and Phase III studies, performed under almost identical protocols, demonstrate the device is safe and effective for the treatment of symptomatic atrial fibrillation.

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[f] Irvine Biomedical, Inc. IBI Therapy™ Cardiac Ablation System (P040014); Biosense Webster, Inc. Biosense Webster NaviStar™/Celsius™ ThermoCool® Diagnostic/Ablation Deflectable Tip Catheters (P030031, P040036); CryoCath Technologies, Inc. 7F Freezor® Cardiac Cryoablation catheter and CCT.2 CryoConsole System (P020045); Boston Scientific Corporation Blazer II XP™ Cardiac Ablation Catheter, EPT-1000 XP™ Cardiac Ablation Controller (with software version 3.12) (P020025); C.R. Bard Stinger™ Ablation Catheter and TempLink™ Extension Cable (P000020); St. Jude Medical Livewire® Catheter Ablation System (P960016); Cordis Corporation Webster Diag./Ablation Deflectable Tip Catheter (P950005); Medtronic Cardiorhythm ATAKR™ RFCA System (P930029); EP Technologies, Inc. EP Tech Cardiac Ablation System (P920047).

- Cardima submitted a full array of safety and effectiveness data to justify approval.

- The REVELATION® Tx Microcatheter Ablation System represents an important, effective and safe treatment option for electrophysiologists to offer their patients with paroxysmal AF who do not have another option.

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