CLINICAL REVIEW OF PMA

DATE: 12 MARCH 2007

SUBJECT: P020039 AND AMENDMENTS

SPONSOR: CARDIMA, INC.

DEVICE: REVELATION® TX MICROCATHETER WITH NAVABLATOR ABLATION SYSTEM

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Section 1.0 PMA background

1.1 PROPOSED INDICATIONS FOR USE: "The Cardima® Inc., REVELATION® Tx Microcatheter with NavAblator RF Ablation System is indicated for treatment of Atrial Fibrillation 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 in the right atrium.

The REVELATION® Tx is intended for the creation of continuous linear lesions for the purpose of interrupting arrhythmia pathways. The NavAblator™ is intended for the creation of lesions at the isthmus for the purpose of interrupting arrhythmia pathways when the REVELATION Tx is not used to complete the isthmus region."

1.2 DEVICE DESCRIPTION:

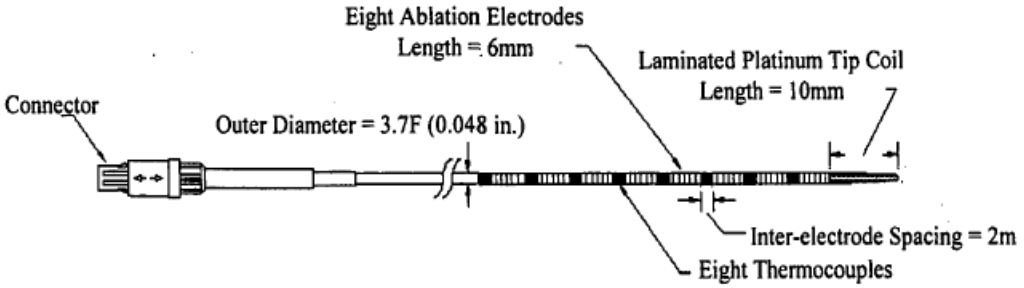
The device is an ablation system composed of the Revelation® Tx, micro radiofrequency (RF) ablation catheter, the NavAblator™, a standard 8F RF ablation catheter and the Naviport Guiding catheter.

The Revelation Tx is a single use, steerable, multi-electrode ablation microcatheter (3.7F) with a flexible non-electrically active platinum coil tip. It has eight ablation electrodes and eight thermocouples near the distal end of the catheter. Each electrode uses the thermocouple just proximal for temperature feedback control of RF energy to maintain a pre-selected set temperature.

The ablation electrodes are 6mm in length and are composed of coiled 0.005" diameter platinum wire. This design has a higher risk of coagulum formation compared to standard RF catheters due to the "edge effect" which concentrates radiated energy at sharp geometric gradients[1,2,3]. Coagulum is a concern because it can interfere with the efficiency of energy transfer or heating of the tissue and therefore decrease the size of the ablation lesion and also coagulum can break off the catheter and embolize[4].

Radiofrequency energy is applied to each electrode individually. The catheter is designed to produce thin linear radiofrequency ablation lines. It is intended to be used with a deflectable guiding catheter (Naviport) to properly position the distal tip.

Diagram of Revelation Tx



The NavAblator is an 8F single use radiofrequency ablation catheter with four electrodes. The distal electrode is a 4mm ablation electrode with a thermocouple sensor.

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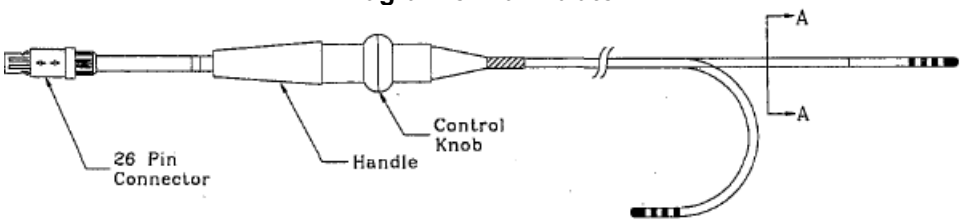
[1] McRury ID, Panescu D, Mitchell MA and Haines DE "Nonuniform heating during radiofrequency catheter ablation with long electrodes" Circulation 1997;96:4057-4064

[2] Chan EKY, Abati AL and Vepa K "Coagulum index predicts coagulum formation in right atrial radiofrequency energy delivery to ablate atrial fibrillation" PACE 2000;11:1856-1856

[3] Weiss C, Antz M, Thuneke F, Meinertz T, Kuck KH and Willems S "Radiofrequency catheter ablation using long coiled electrodes: Impact of irrigation on lesion dimensions and incidence of coagulum formation" PACE 2001;24:933-938

[4] Wittkampf FHM and Nakagawa H "RF Catheter ablation : Lessons on lesions" PACE 2006;29: 1285-1297

Diagram of NavAblator



The Naviport Guiding catheter is a deflectable guiding catheter in French sizes 8F to 11F designed to facilitate proper positioning of the Revelation Tx. It has two lumens, one for the device and the other a closed pull wire lumen. The Naviport is a legally-marketed device, cleared previously under a 510(k).

The ablation system requires a RF generator. Cardima does not produce a generator so a RF generator with compatible parameters would be used. The RF generators used in the clinical study were the Radionics RFG-3E and IBI 1500T.

Section 2. Clinical study background

2. 1 HISTORY

The Revelation Tx catheter was designed to create continuous linear radiofrequency ablation lesions. Cardima developed the ablation procedure based on the surgical Maze procedure. They wanted to investigate whether lines of block placed only in the right atrium could provide treatment of atrial fibrillation. The position of the lines was based on both the Maze procedure and feasibility studies in Europe. The US investigational device exemption (IDE) clinical trial was conducted over many years but the protocol always contained the same description of the ablation procedure required to be performed with the same location for the ablation lines. The protocol dictated collection of acute procedural data through out the study.

The clinical study began in December 1997. It was a multi-center, prospective, non-randomized unblinded single arm study. The study was conducted in three phases. These phases were Feasibility or phase IIa, Expanded Feasibility or phase IIb and Pivotal or phase III.

Study phase	# sites	# patients treated
IIa	3	10
IIb	9	38
III	14	98

Phase IIa was a true feasibility study looking at the feasibility of the procedure and initial safety to determine if the study could be expanded.

Phase IIb demonstrated that the Revelation Tx was not effective in creating the cavo-tricuspid isthmus (CTI) lesion in many patients. As a result, investigators were using non-protocol ablation catheters to complete the ablation procedure. Cardima was informed by the FDA in many letters, emails and meetings (see appendix 7) that patients in whom the use of a non-protocol (non-investigational) device was required to complete the ablation procedure would be deemed a chronic failure. Cardima added a 4mm tip ablation catheter, the NavAblator, to the investigational protocol in order to have a device system that could complete the ablation procedure. The addition of this catheter was the major difference between phase IIb and phase III.

The procedures in phase III were performed between September 2000 and August 2003.

Cardima submitted the original PMA in 2002. The pivotal trial was ongoing at the time of the submission. The original PMA submission contained the results of 38 patients in Phase IIb as well as 78 patients from phase III.

The Circulatory System Devices Advisory Panel met on May 29 2003 to discuss the original PMA submission. The panel members voted unanimously 7 to 0 to recommend that the device system be found not approvable. FDA sent a not approvable letter to Cardima on 6/26/03.

The company submitted an amendment (Amendment six) in January 2004 reporting on most of the patients in the Phase III. Cardima requested that the pivotal trial was to be the basis for the review of their ablation system. Amendments 1-5 to the PMA were submissions addressing FDA questions or making minor changes.

Amendment six contained a re-analysis of patient compliance with event recording and a re-analysis of the chronic clinical success of the ablation procedure. Cardima reported on 98 patients that had ablation in Phase III and verified data on 93. 84 patients had completed at least six months follow-up. The protocol states that the sample size of 80 patients in Phase III will allow the characterization of clinical success using confidence interval estimation.

FDA reviewed the data in Amendment six and concluded that the concerns and questions about the Cardima ablation system remained unanswered. These were:

1. Acute procedural effectiveness of the Cardima ablation system can not be determined because the protocol specified data was not collected. Without knowing if the patient actually received the ablation treatment the ultimate clinical outcome can not be attributed to the Cardima ablation system.
2. The measurement of chronic clinical effectiveness was flawed because of possible over-counting symptomatic atrial fibrillation episodes at baseline and undercounting of episodes at six months post ablation procedure.
3. A risk-benefit profile can not be produced because it is not possible to determine effectiveness.
4. The NavAblator catheter was not successful in producing bidirectional conduction block at the cavo-tricuspid isthmus in sufficient numbers of patients. The NavAblator did not meet the performance criterion routinely used by the FDA to evaluate catheters used to create cavo-tricuspid isthmus conduction block.

A not approvable letter was sent to Cardima on May 21, 2004.

There have been several meetings of FDA and Cardima after the latest not approvable letter but no additional patient data were submitted.

2. 2 SUMMARY OF CLINICAL PROTOCOL, PHASE III PIVOTAL

The study was a single arm unblinded investigation. All patients underwent right atrial linear ablation in an effort to reduce the frequency of symptomatic atrial fibrillation.

Trial entry criteria

Inclusion criteria

- Documented symptomatic paroxysmal atrial fibrillation (a fib) refractory to at least two anti-arrhythmic drugs (if amiodarone is used first, patient may be refractory to amiodarone alone and entered into the study)
- Frequent, 3 or more, symptomatic episodes during the 30-day baseline period
- Between 21 and 80 years
- Informed consent and can follow protocol
- Normal sinus rhythm at the time of the procedure or can be converted

Exclusion criteria

- Pregnancy
- Prior acute ablation failure within 2 months
- AMI within 6 weeks
- Contraindication or unable to comply with long-term anticoagulation therapy
- Valvular disease, aneurysm or LVH with NYHA Class III or IV
- Known or suspected coagulopathy or bleeding diathesis
- CVA or TIA within 6 months
- Intra-cardiac thrombus
- Echocardiographic PFO or ASD
- LA dimension > 5 cm

The number of self reported symptomatic atrial fibrillation (AF) episodes during a baseline period of 30 days was compared to the number of self reported symptomatic AF episodes during another 30 day period six months after the ablation procedure with the two investigational catheters. The patient was to carry a transtelephonic monitor (TTM) with them during the two 30 day periods and record during all symptoms. These recordings were then transmitted by telephone to a monitoring service. Each transmission was classified by the monitoring service cardiologist as being AF or another rhythm. The monitoring service was blinded to the ablation or enrollment status of the patients.

Each patient was required to have at least three documented AF episodes transmitted in the baseline period to be eligible for ablation with the Cardima catheters. If they did not have three episodes in 30 days they could undergo an additional 60 day monitoring period. To be considered for enrollment they would need a total of 9 episodes in the total 90 days, which would be an average of three per 30 days.

Baseline observation period

Each patient was given an event recorder for the 30 day baseline period. They were instructed to carry the event recorder with them and record whenever they had symptoms of atrial fibrillation. The patients were also required to transmit weekly even if they were not symptomatic. To be considered for ablation in the study the patient must transmit a minimum of three episodes of AF in the baseline period. Patients were not told the number of episodes required to be considered for ablation but they were aware that a certain threshold needed to be reached in order to be considered for ablation with the investigational device.

Patients who fail the initial screening were allowed to rescreen. They were then required to have 9 total episodes in 90 days, which would average to be 3 per month. The re-screening period was 60 additional days.

Ablation procedure

All patients were heparinized with ACT maintained at 200 – 300 seconds. Before each ablation burn the investigator recorded bipolar electrograms and pacing thresholds in sinus rhythm to determine good tissue contact. “In general, unless the electrodes are in the superior or inferior vena cava, pacing thresholds of less than 5.0 mA indicate adequate tissue contact of both electrodes in the pair.” Phrenic nerve proximity was determined by a pacing protocol.

The Revelation was used to “Apply RF along three trajectories (posterolateral, posteroseptal and along the isthmus) a fourth trajectory (anterior) may be included at the option of the investigator.” “The NavAblator catheter is optionally available for ablation of the isthmus only after first attempting to create a linear burn with the Revelation Tx.”

The RF energy is delivered to each of the individual eight electrodes of the Revelation Tx for 60 seconds. RF energy is be delivered to each of the electrodes in good contact one at a time to form the line of ablation. The investigator is then instructed to move the catheter to “overlap the gap”. For each application of energy there is to be a recording made of the atrial electrogram pre and post ablation

burn. The electrogram recordings were to be sent to Cardima. A core laboratory was to perform a blinded analysis of these recordings to provide an objective assessment of procedural success per patient.

The clinical trial protocol addresses the risk of coagulum formation by instructing the physician to carefully inspect the catheter for coagulum if there is an impedance rise or if there is a cause to believe coagulum could be present at any point in the ablation procedure. The protocol instructs the physician that "loosely adherent thrombus may be carefully cleaned off the catheter electrodes with saline." The protocol warns against applying force to the catheter. There is no instruction as to the number of times that the Revelation can be removed and re-inserted or the number of times that the catheter can be safely cleaned without damage to the catheter.

Endpoints of the trial

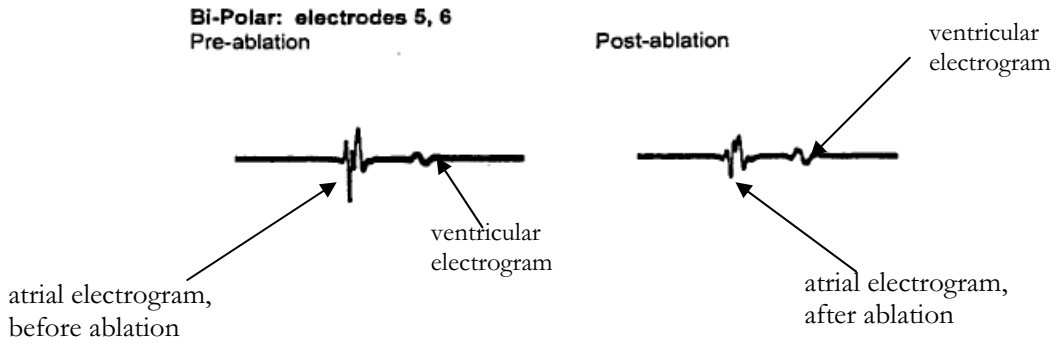
Procedural success: "The procedural effectiveness of the Revelation™ Tx will be established based on achieving the following outcome:

> Demonstration of at least one of the following conditions at the line(s) of ablation during sinus rhythm: a) reduction in the amplitude, fragmentation or widening of local electrograms; b) appearance of split potentials; or, c) increase in pacing threshold."
> The requirement of pacing thresholds was eliminated between Phase IIb and III.

The protocol states in section 4.4, page 31 that "electrogram amplitude is considered an objective measure. Intraprocedure electrograms will be printed on recording paper with calibration marks and sent to a single core laboratory for determination of pre- and post-ablation amplitudes. The core laboratory review will be blinded to the subject identity, site, and whether the electrogram was obtained pre-or post-ablation."

The selection of the acute procedural endpoint was based on pre-clinical animal studies. These studies showed that the Revelation Tx was capable of creating continuous, linear transmural lesions from sequential electrode ablations. And that a set temperature of 50-55° 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.

Example of electrogram recording from pre-clinical study (atrial ablation in goats) first reported to FDA in Original IDE #G970280 dated 11/18/97, excerpted from engineering module of the PMA



Each patient was to be classified a procedural success or failure of the use of the Revelation Tx catheter after determining the change in the size of the atrial electrogram for each of the electrodes used. A successful line was one in which each electrode used to create an ablation lesion (a burn) created this change in atrial electrogram amplitude. For example, if eight of the eight electrodes were used there would be eight paired measurements to analyze to determine if that line was successful.

The acute procedural endpoint for the NavAblator catheter was the demonstration of bi-directional conduction block at the cavo-tricuspid isthmus.

Primary clinical effectiveness endpoint: Reduction in frequency of symptomatic episodes during the 6th month of follow-up compared to the baseline frequency while "either maintained on the same anti-arrhythmic drug regimen or a reduced dosage." If subjects had ≥ 5 episodes in the 30 day screening period they were required to have a reduction of 50% or more to be called a success. If there were 3-4 episodes during the baseline period, a reduction of 75% was required to be called a success.

Section 4.2 of the protocol states that "Subjects electing to receive implantable pacemakers prior to the six month follow-up will be considered failures."

Secondary effectiveness endpoint: improvement in the quality of life measured by SF-36 and the Atrial Fibrillation Severity Scale (AFSS) compared to baseline

Safety endpoint: The safety endpoint was listed as incidence of complications; major complications in the first 7 days post ablation and adverse events in the 24 months follow-up period. No threshold was included in the protocol.

Follow-up

The patient was instructed to transmit weekly rhythm strips during month one, month three and month six, even if the there were no symptomatic episodes. In other words the patients were required per the protocol to transmit four or more transmissions in the first month and in months three and six.

The weekly transmissions were planned to help encourage patient compliance with the recordings and to ensure that the recorders were still functioning. The patient was to be contacted prior to the 30 day period by the study coordinator and reminded to begin the routine and symptomatic transmissions.

The Quality of Life questionnaires were administered by the study coordinator for each site. They were given to the patients and were usually completed at that visit. Some patients took the forms home to fill out. If the forms were not returned the coordinator completed the form for the patient in a telephone interview.

2. 3 DIFFERENCES BETWEEN PHASE IIB AND PHASE III

Differences between the Expanded Feasibility phase (IIb) protocol and the Pivotal phase (III) protocol included:

1. Phase III added the NavAblator catheter to complete the linear lesion set dictated by the protocol
2. The requirement to measure pacing thresholds pre and post ablation was removed for Phase III. The protocol does not mention measurement of bi-directional block but on page 73 of the submission it states "It must be noted that bi-directional block is the primary indicator of procedural success for the isthmus line".

3. Stress test specified in phase IIb was Masters step. Phase III allowed substitution of treadmill stress.
4. Holter monitor removed from the protocol between Phase IIb and Phase III.
5. The age limit for Phase III was increased to 80 years from 75 years

Section 3. Study results

3.1 PATIENT ACCOUNTABILITY AND DEMOGRAPHIC INFORMATION

The initial PMA application reported the results of 116 patients from Phases IIb (Expanded Feasibility) and III (pivotal) who had undergone the ablation procedure. PMA Amendment six dated January 2004, reported the results of phase III only.

study phase	# sites	# patients treated
IIa	3	10
IIb	9	38
III	14	93 procedure cohort (84 with 6 month follow-up are effectiveness cohort)

There were 98 patients who had ablation with the investigational device system in phase III but five did not have verified procedure data. Therefore Cardima identified 93 patients of phase III as the procedure cohort. The 84 patients with sufficient baseline AF episodes who completed 6 months follow-up are classified as the effectiveness cohort. This memo will also report the data from phase IIb where appropriate, such in the discussion of adverse events.

The patients were monitored for 30 days and must have had at least three documented symptomatic atrial fibrillation (AF) episodes during this baseline period to be considered for the ablation procedure. There were 6 patients (2 in phase IIb, 4 in phase III) whose screening rhythm strip diagnoses were disputed when reviewed by the monitoring service cardiologists but they had already been ablated at that point.

64 patients in phase III had at least 12 months follow-up and 30 had 24 months follow-up.

Demographics phase III

	n (%)	mean age	age range
men	69/93 (74.2)	56.8 ± 10 years	28 to 78 years
women	24/93 (25.8)	62.2 ± 9.8 years	42 to 77 years
all patients		58.2 ± 10.2	

76% of the patients had concomitant heart disease, although none had significant structural heart disease. 68 patients (68/92 or 73.9%) were NYHA class I and 24 (24/92 or 26.1%) patients were class II.

8 patients had a pre-existing pacemaker prior to enrolling in the study.

30 patients in phase III had had a previous ablation procedure; 24 for atrial flutter, 7 for AF and 4 other.

3. 2 INVESTIGATIONAL SITES

Investigator list from original PMA

Table F-6, List of Investigators and Subjects Treated

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. Marinchak, 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 Warren, NJ	III	4
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

Investigator list from A6

Table 13. List of principal investigators, study sites and number of ablations included in study report.

Site ID	Principal Investigator	Clinical Investigational Site	Number of Procedures
1	Sung H. Chun, MD	Stanford Medical Center Stanford, CA	0
3	Hugh Calkins, MD	The Johns Hopkins Hospital Baltimore, MD	2
5	Ted D. Friehling, MD	Inova Institute for Research and Education Falls Church, VA	8
6	Roger A. Marinchak, MD Douglas B. Esberg, MD	Main Line Health Heart Center Wynnewood, PA	4
8	Bruce G. Hook, MD	New England Heart Institute Manchester, NH	1
9	Seth J. Worley, MD	Lancaster Heart Foundation Lancaster, PA	0
10	Timothy M. Talbert, MD	Diagnostic Center Chattanooga, TN	8
11	Sanjeev Saksena, MD	EHI-Atlantic Health System Cardiac Medicine & Electrophysiology Warren, NJ	4
14	Abraham G. Kocheril, MD	Carle Heart Center Urbana, IL	19
15	Larry A. Chinitz, MD	NYU Medical Center New York, NY	1
16	Imran K. Niazi, MD	Wisconsin Center for Clinical Research Milwaukee, WI	15
17	Jose Nazari, MD	Cardiac Arrhythmia Consultants Chicago, IL	4
18	Randy A. Lieberman, MD	Harper University Hospital Detroit, MI	5
19	Roger A. Winkle, MD	Sequoia Hospital Redwood City, CA	4
21	Eli S. Gang, MD	Access Clinical Trials Beverly Hills, CA	5
23	Arjun D. Sharma, MD	Regional Cardiology Associates Sacramento, CA	15
		Total	95

Five additional subjects have undergone ablation in the last four months, but their data are not included in the analyses performed in this study report.

Eleven sites in phase III enrolled < 10 patients and three sites enrolled 15 or greater. The three largest sites enrolled 49/95 or 51.5% of the total patients in phase III.

3.3 PROCEDURE DATA

There was verified data on 93 patients who underwent 95 ablation procedures with the Cardima system in phase III.

The mean procedure time was 218 ± 111 minutes, maximum procedure time ranged from 131 to 549 minutes across investigational sites. The mean fluoroscopy time was 43 ± 42 minutes.

The case report forms for the procedural data were designed to collect the details of the use of the investigational catheters but there is a large amount of missing data.

Missing data includes:

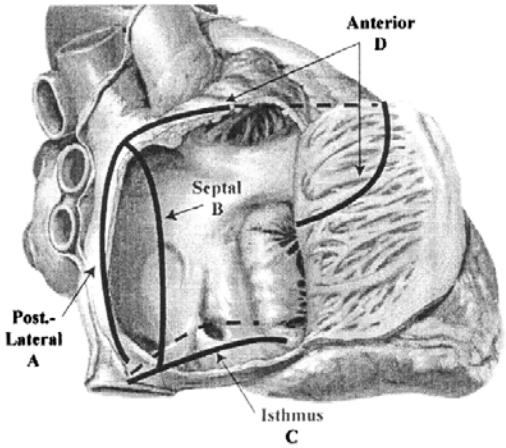
1. the total number of RF energy applications in the study

2. number of RF energy applications per patient and per electrode on the Revelation Tx
3. number of energy applications with the NavAblator catheter
4. the number of instances of coagulum noted or impedance rise
5. average actual temperature seen with ablation
6. atrial electrogram measurements per ablation electrode used

3. 4 ABLATION PROCEDURE PERFORMED AND WITH WHAT DEVICE:

Three or four linear lesions in the right atrium were part of the initial ablation protocol in phase IIb and the early part of phase III. If a patient had had a previous cavo-tricuspid isthmus ablation procedure the investigator could eliminate that lesion. The locations of the lesions were: postero-lateral (A), septal (B), tricuspid isthmus (C) and anterior (D). The anterior line of lesions was taken out of the protocol early in phase III because of the risk of sinus node damage.

The study protocol states that "The NavAblator™ catheter is optionally available for ablation of the isthmus only after first attempting to create a linear burn with the REVELATION Tx."



Cardima states on page 79/293 of A6 "In all study procedures, Revelation Tx alone was used to create linear lesions in the right atrium." But the review of the CRF and source documents[5] of patient 0606

[5] Electrophysiology Report, Lankenau Hospital Cardiovascular Services, date: 10/24/2001

line. The Navablator catheter was then exchanged for a 4.3F Revelation TX catheter inserted through a 30 mm Naviport catheter and positioned along the intracaval posterior lateral right atrium and the septal right atrium to deliver a series of RF energy applications to create a linear lesion in both regions. Following this the Revelation TX catheter was removed and the Navablator catheter was reinserted and positioned on either side of the intercaval and septal ablation lines to determine whether conduction block was present. Several gaps in conduction block were verified at both lines and additional RF energy applications were delivered to these sites with focal RF energy applications of 60 seconds each at power settings titrated to thermoster temperatures of 55 degrees Centigrade. Following the RF energy applications, bidirectional conduction block and the intercaval ablation line was verified. Conduction block was also verified in the body of the septal conduction line except for residual conduction running superiorly in the superior vena cava atrialized portion of the right atrium which could not be accessed due to the position of the Ensite mapping balloon catheter.

showed that mapping performed after ablation with the Revelation Tx showed gaps in the line of lesions. The NavAblator catheter was used to ablate gaps in the lesion set created with the Revelation Tx in that patient.

Because of the large amount of missing data, it is unknown how many other patients required the use of the NavAblator or any other catheter to complete the septal or lateral right atrial lesions.

If the Revelation Tx was unable to produce a successful line of block at the cavotricuspid isthmus the protocol allowed the use of the NavAblator to complete that line of block.

Catheters used to make line of block at the cavotricuspid isthmus

Catheters	**Number of patients (%)**		
	Phase IIb n=33	**Phase III n=89**	**Total N=122**
NavAblator only	n/a	51 (57.3)	51 (41.8)
Revelation Tx only	14 (42.4)	8 (9.0)	22 (18.0)
Other only	12 (36.4)	4(4.5)	16 (13.1)
Revelation Tx, other	7 (21.2)	n/a	7 (5.7)
Revelation Tx, NavAblator, other	n/a	3 (3.4)	3 (2.5)
NavAblator, other	n/a	20 (22.5)	20 (16.4)
Revelation Tx, NavAblator	n/a	3 (3.4)	3 (2.5)

Other catheters used were: Blazer II, Navistar, Marinr, Chilli and the Stinger

Twenty-seven procedures out of the 95 total in phase III (28.4%) required a non-investigational catheter to be used because the investigational catheter system failed to reach the acute procedural endpoint for the cavo-tricuspid isthmus lesion.

3. 5 MEASUREMENT OF PROCEDURAL SUCCESS

All FDA pre-approval clinical trials of ablation catheters have required pre-specified acute procedural success endpoints. The specific acute procedural endpoints are chosen to measure what each sponsor claims their ablation catheter can ablate.

The fundamental importance of the procedural success assessment is to know whether or not the individual received the treatment and that the device was used in the same way in all patients in the clinical trial.

It is not sufficient to merely insert and activate the investigational ablation catheter, it is necessary to know whether or not the patient received successful ablation. Without this knowledge it is impossible to attribute clinical change to the use of the ablation catheter.

Acute procedural endpoints are essential for assessing device safety and effectiveness. They are necessary to:

1. Assess whether or not the individual truly received the treatment
2. Determine if the device was used in the same way in all patients in the clinical trial

3. Clearly identify the goal of the ablation procedure to the investigator and to let the investigator know when the procedure is finished (when they can stop applying ablation lesions)
4. Determine if all patients respond to the device in a similar fashion
5. Measure the claims of what the sponsor believes that their ablation system can do acutely (show that what the sponsor says that their catheter burns or freezes is actually burned or frozen)
6. Identify potential safety issues
7. Identify acute procedural endpoint issues associated with decreased effectiveness
8. Instruct the physician in how to appropriately and safely perform the ablation.
9. Provide data that the FDA can use to write labeling/instructions to help physicians achieve the same results as were seen in the premarket trial
10. Assure that use of the device as per the Instructions For Use (IFU) predicts clinical success

Each patient can be classified as an acute success if it is shown that the device met the acute procedural success endpoint. In order to determine whether or not the ablation device system is effective there needs to be chronic clinical success in the patient that had a successful ablation procedure. A patient can not be a chronic effectiveness success of the trial if the ablation catheter system was not able to be used to create the prespecified procedural success.

Results of acute procedural endpoint in phase IIb

catheter	# patients	%patients with procedural success
Revelation Tx	38	unknown
NavAblator	0	not applicable

Results of acute procedural endpoint in phase III

catheter	# patients	%patients with procedural success
Revelation Tx	93	unknown
NavAblator	77	62.3% (50.6%, 73.1%)

Acute success of the RevelationTx catheter

The data required to measure the acute effectiveness of the procedure per patient was not collected.

Cardima reports a small number of paired electrogram measurements but the data required to determine if any patient received an effective set of ablation lesions is not available.

Cardima states that reduction of amplitude of electrograms at the lesion site of ≥50% indicates a transmural lesion for the Revelation Tx catheter. Per page 81/293 of amendment 6 "the study Protocol required investigators to document a proxy measure: reduction of the amplitude of atrial electrogram amplitudes after ablation. The protocol required documentation of paired before- and after-ablation measurements for each electrode for each lesion created." Cardima and the FDA agreed on this procedural success criterion as a proxy for actually measuring a line of block created by the Revelation Tx.

After the Revelation Tx was positioned to the satisfaction of the investigator (good electrogram signal and good pacing thresholds) an electrogram measurement from the ablation electrode was to be recorded, then an application of energy or burn was performed and then another measurement of the atrial electrogram. This change in electrogram size per burn was to give the investigator information about the success of ablation *for that electrode.* These paired electrogram measurements were to be made for each burn for each electrode. The patient could be considered to have had a successful procedure if all the paired measurements showed the required decrease in electrode amplitude. If the amplitude did not decrease or did not decrease sufficiently the investigator could then create another burn with that electrode.

The determination of successful creation of both posterolateral and septal lines using the Revelation Tx catheter required the evaluation of the paired measurements for each electrode used to create a burn.

A successful ablation line is one in which each application of energy at each electrode used (of the eight possible) results in electrogram amplitude reduction. For each line all the electrodes in good position are to be used once and then the catheter is repositioned to fill in gaps that would necessarily occur between the electrodes used. There is a space of 2mm between each of the 8 electrodes of the catheter. Therefore in each patient the sequence of electrodes on the Revelation Tx was to be used at least twice for both the postero-lateral and the septal ablation lines or four total times, because if the catheter was not moved there would be a gap in the line created.

There are eight electrodes on the Revelation Tx that could be used to deliver RF ablation energy if each electrode was in good contact with atrial tissue. If the investigator used each electrode for each ablation line there would be 32 burns per patient (16 for the septal and 16 for the posterolateral). There would then be 64 atrial electrogram amplitude measurements performed or 32 pairs. If this same procedure was performed on each patient there would be a total of 5952 measurements (93x64=5952) or 2976 pairs.

Missing acute procedural endpoint data

site of lesion	number of patients	number of expected paired measurements per patient	total expected measurements	total reported measurements	# (%) missing measurements	# (%) patients with missing acute procedure endpoint data
lateral	93	16	2976	504	2472 (83)	93 (100)
septal	93	16	2976	424	2552 (85.8)	93 (100)

But the number of measurements per patient would differ depending on clinical circumstance. For example, the CRFs for patients show there were 35 (18 lateral and 17 septal) and 38 (22 lateral and 16 septal) burns from the Revelation Tx respectively. Therefore in these patients the catheter electrodes were required to be used more than twice. For these two patients there should have been 70 (36 +34) and 76 (44 +32) atrial electrogram measurements. Or stated another way, for patient who had 18 burns to the lateral right atrium there should have been 18 pairs or 36 electrogram measurements. And for the 17 septal burns there should have been 17 pairs or 34 electrogram measurements. The total for patient would be 70 measurements or 35 paired comparisons.

Revelation Tx burns from patients

	tient	patient
number of lateral energy applications (burns)	18	22
number of septal energy applications (burns)	17	16
total number of burns	35	38
total number of atrial electrogram measurements (pre and post ablation) to be made per protocol	70	76
number of paired comparisons needed to determine if the patient had a successful ablation line completed	35	38

If these two patients are used to calculate the total number of atrial electrogram measurements for phase III, there should have been 95 procedures times 70 measurements or a total of 6650 measurements of atrial electrograms or 3325 paired.

Cardima reports the results of 928 measurements. They report pooled measurements across the entire patient cohort. The comparison of mean electrogram amplitude before and after ablation is meaningless.

No patient was identified as having a successful set of linear lesions created by the Revelation Tx catheter.

It is stated clearly in both the original and amended PMA submissions that the required prespecified acute procedural measurements were not collected.

There was no evidence in the submission that any patient had all the required measurements per line of lesions that would be needed to determine if a patient had a successful use of the investigational catheter.

It is unknown how many patients had a successful ablation procedure with the Revelation Tx. Therefore it is impossible to know if the treatment or chance caused the outcome of the patient at the time of measurement of the chronic clinical endpoint.

Furthermore, because the measurement of acute procedural success was incompletely recorded there is no assurance that all the investigators used the same method to determine procedural success or to determine if the ablation lesion had been successfully produced. It is possible that the procedure performed by different investigators was slightly or substantially different from each other.

Therefore, even if the Cardima ablation system met the primary effectiveness endpoint the absence of the acute procedural endpoint data would make the system not approvable due to the inability to write sufficient instructions for use based on results of the clinical trial.

<u>Acute success of the NavAblator catheter</u>
Bidirectional block at the cavo-tricuspid isthmus is the acute procedural endpoint for the catheter used for that lesion. In phase III there were 77 patients in whom the NavAblator was used to ablate the cavo-tricuspid isthmus. 48/77 or 62.3% had successful demonstration of bidirectional conduction block without the use of a non-investigational catheter.

The objective performance criteria for this lesion set is 90% of patients would have successful creation of bidirectional conduction block with a lower bound of 80%.

Twenty-seven patients required the use of a non-investigational catheter to complete the ablation procedure. Documentation of the agreement to classify all patients that required treatment with a non-protocol or non-investigational device is available in the appendix in Section 7b of the panel pack.

3. 6 BASELINE ATRIAL FIBRILLATION EPISODE ASSESSMENT

Patients were given a transtelephonic monitor (TTM) and told to record whenever they had symptoms that they thought were atrial fibrillation. Transmissions were evaluated to determine if they were actually atrial fibrillation.

In the original PMA submission the percentage of confirmed atrial fibrillation per patient ranged from 12.9 to 100%. These results confirm what has been described in the medical literature. Patients usually have both symptomatic and asymptomatic episodes and they are frequently poor at determining which symptoms are due to atrial fibrillation[6,7].

Cardima acknowledged that there was no attempt to determine if the transmissions represented discrete events. The FDA believes that it is possible that one atrial fibrillation episode could have triggered more than one transmission in some patients therefore over-reporting the number of symptomatic episodes.

3.7 COMPLIANCE WITH EVENT RECORDING AT THE 6TH MONTH

The investigational protocol states that patients are to record symptomatic episodes when they occur and also send mandatory weekly transmissions in the 6th month even if there are no symptoms.

Cardima submitted detailed 6th month post-procedure transmission data on 83 patients in the original PMA. 22 patients did not transmit any transmissions in the 6th month follow up period. At least 2 patients were known to have lost the monitor or to have a non-functioning monitor.

Transmissions in the 6th month post ablation reported in the original PMA (phase IIb and initial patients from phase III)						
Transmission number	**0**	**1**	**2**	**3**	**4**	**>4**
Number of patients	22	5	17	9	16	14

22/83 patients had no transmissions or 26.5%. 31/83 patients had 1-3 transmissions in the six month or 37.3%. A total of 53/83 (63.9%) patients had poor compliance with the primary effectiveness assessment method in the original PMA submission.

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[6] Page RL, Wilkinson WE, Clair WK, McCarthy EA, Pritchett ELC "Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia" Circulation 1994;89:224-227

[7] Hindricks G, Piorkowski C, Tanner H, Kobza R, Gerds-Li J, Carbucicchio C and Kottkamp H "Perception of Atrial fibrillation before and after radiofrequency catheter ablation" Circulation 2005;112:307-313

The FDA was concerned about compliance with the TTM recordings both because the primary endpoint of the trial is dependent on the accuracy of this data recording but also because it is well known that poor compliance with long term recording regimens is common[8]

Cardima reanalyzed the transtelephonic transmission data for amendment six. They found that in the original PMA submission TTM transmissions were reported for days 151-180 after the ablation procedure. They also found that the start date of the sixth month monitoring period was not recorded in the CRFs, therefore the day that the study monitor alerted the patient as to the onset of the sixth month weekly required transmissions was not known. Cardima elected to use "a computer-based algorithm to identify the 30-day period closest to the midpoint of the sixth month after ablation in which episode monitoring was maximal."

Patients completing event monitor transmissions in the sixth month

# patients at six months follow-up	# patients completing required transmissions	% missing
84	60	28.5

Table 41. Distribution of number of event monitor transmissions in the third and sixth months of follow-up (N=84).

	Month 3		Month 6	
Number of Transmissions	Frequency	%	Frequency	%
0	2	2.4	7	8.3
1	4	4.8	1	1.2
2	7	8.3	7	8.3
3	9	10.7	9	10.7
4 or more	62	73.8	60	71.4
Total	84	100.0	84	100.0

The new analysis of the TTM transmissions at six months results in an improved calculated compliance rate but the FDA would consider only 60/84 (71.4%) patients to have good compliance with this requirement of the protocol.

[8] Pritchett E "Symptomatic arrhythmia recurrence as an outcome in clinical trials of antiarrhythmic drug therapy" Heart Rhythm 2004;1:836-840.

3. 8 CHRONIC CLINICAL EFFECTIVENESS

The number of patients who had a procedural success with the Revelation Tx cannot be adequately assessed. The ultimate clinical outcome of the patients can not be correlated with success or failure of the procedural use of the investigational device system.

Even if the FDA can not describe how the catheter system was used in the procedure (how many lesions required per patient, how much energy was required, what temperature and power were used, was one linear lesions easier to perform than the other, how many patients actually had a linear lesion made) can they assume that the investigators used the catheters effectively based on the chronic effectiveness results?

The placebo effect rate in this trial can not be measured as there was no control group. Placebo effects in the range of 30 to 40% are frequently reported in cardiovascular device trials.[9,10,11] Randomized antiarrhythmic drug trials in symptomatic paroxysmal atrial fibrillation have reported event free rates at six months in the placebo group of 35 -45%[12,13,14] Freedom from symptomatic atrial fibrillation at one year follow-up has been reported to be 16-29% of placebo groups [15,16]

The chronic effectiveness endpoint of the trial was subjective. Patients had to recognize that they were having symptoms possibly due to AF and record the rhythm with the event recorder at that time. Therefore the patient would have to had a working event recorder with them and be able to use it. It is well known that patients are poor at recognizing symptoms of AF[17,18] and this was confirmed in this premarket study. It is also known that reporting of symptoms is affected by AF procedures. [19,20]

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[9] Rana JS, Mannam A, Donnell-Fink L, Gervino EV, Selke FW and Laham RJ "Longevity of the placebo effect in the therapeutic angiogenesis and laser myocardial revascularization trials in patients with coronary heart disease" American Journal of Cardiology 2005; 95:1456-1459

[10] Leon MB, et al " A blinded, randomized, placebo-controlled trial of percutaneous laser myocardial revascularization to improve angina symptoms in patients with severe coronary disease" Journal of the American College of Cardiology 2005;46:181201819

[11] Mehra MR, Greenberg BH "Cardiac resynchronization therapy; caveat medicus!" Journal of the American College of Cardiology 2004;43:1145-1148

[12] Patten M, Maas R, Bauer P, Luderitz, Sonntag F, Dluzniewski M, Hatala R, Opolski G, Muller, H and Meinertz "Suppression of paroxysmal atrial tachyarrhythmias-results of the SOPAT trial" European Heart Journal 2004;25:1395-1404

[13] Bellandi F, Simonetti I, Leoncini M, Frascarelli F, Giovannini T, Maioli M and Dabizzi R "Long term efficacy and safety of propafenone and sotalol for the maintenance of sinus rhythm after conversion of recurrent symptomatic atrial fibrillation" American Journal of Cardiology 2001;88:640-645

[14] Atarashi H, Inoue H, Fukunami M, Sugi K, Hamada C and Origasa H "Double-blind placebo-controlled trial of aprindine and digoxin for the prevention of symptomatic atrial fibrillation" Circulation Journal 2002;66:553-556

[15] Lafuente C, Mouly S, Longas-Tejero MA, Mahe I and Bergmann JF "Antiarrhythmic drugs for maintaining sinus rhythm after conversion of atrial fibrillation" Archives of Internal Medicine 2006;166:719-728

[16] Hemel N "Quinidine rehabilitated and more lessons from the PAFAC and SOPAT anti-arrhythmic drug trials for the prevention of paroxysmal atrial fibrillation" European Heart Journal 2004;25:1371-1373

[17] see reference six

[18] Vasamreddy CR, Dalai D, Dong J, Cheng A, Spragg D, Lamiy SZ, Meininger G, Henrikson CA, Marine J, Berger R and Calkins H "Symptomatic and Asymptomatic atrial fibrillation in patients undergoing radiofrequency catheter ablation" Journal of Cardiovascular Electrophysiology 2006;17:134-139

[19] Nergarch A, Frick M "Perceived heart rhythm in relation to ECG findings after direct current cardioversion of atrial fibrillation" Heart 2006;92:1244-1247

[20] Hindricks G, Piorkowski C, Tanner H, Kobza R, Gerds-Li J, Carbucicchio C and Kottkamp H "Perception of Atrial fibrillation before and after radiofrequency catheter ablation" Circulation 2005;112:307-313

The protocol specifies that for a patient to be classified a clinical effectiveness success they had to have a reduction in frequency of symptomatic episodes during the 6th month of follow-up compared to the baseline frequency while "either maintained on the same anti-arrhythmic drug regimen or a reduced dosage." If patients had ≥ 5 episodes in the 30 day baseline period they were required to have a reduction of 50% or more to be called a success. If there were 3-4 episodes during the baseline period, a reduction of 75% was required to be called a success.

To determine if the number of telephone calls was reduced as a consequence of the ablation procedure all other factors would need to be the same to eliminate the possibility that they may have contributed. Possibly most important, antiarrhythmic medications (AAD) and pacing status should be the same as at baseline.

The use of both rate control medications as well as other antiarrhythmic medications could change the patient's perception of AF events even if the AF was not controlled by the medicine. The classification of patient as a failure after ablation if a new AAD or increased dose is required is consistent with previous premarket clinical trials of other ablation devices.

Pacing may influence the timing or presence of symptomatic episodes and ventricular pacing (VVI or VVIR) has been shown in several studies to worsen atrial fibrillation. Therefore any type of pacing could confound the number of symptomatic episodes.

Another factor possibly contributing to the difference in number of episodes is the circadian variation as well as weekly and yearly patterns known to occur in paroxysmal atrial fibrillation. [21, 22] It is possible that the baseline period occurred during the time of the year that the patient normally had increased symptoms and that the sixth month period occurred during a time of decreased symptoms just based on the temporal variation of AF events.
Cardima identified 47 of the 84 patients ablated who had the target level decrease in transmissions. Cardima also considers two of the seven patients with no transmissions in the new sixth month monitoring period as successes because they reported a positive outcome in their QOL questionnaire at the sixth month visit.

There are at least 19 patients of the 49 that the FDA can not agree could be considered to have met the clinical effectiveness endpoint. These are:

- two patients with no TTM at six months (patients and
- 12 patients with new anti-arrhythmic medications (AAD) (2 a one, 6 flecainide, 2 propafenone, 1 disopyramide, 1 dofetilide) or on increased dose of AAD (2 amiodarone, 1 sotalol)
- 1 patient with AV node ablation 190 days post right atrial ablation
- 2 patients with pacemaker or defibrillator implantation prior to six months

There were 27 patients that required treatment with a non-protocol device to complete the ablation procedure. Cardima and the FDA agreed prior to the submission of the PMA that those patients would be considered effectiveness failures.

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[21] Viskin S, Golovner M, Malov N, Fish R, Alroy I, Vila Y, Laniado S, Kaplinsky E and Roth "Circadian variation of symptomatic paroxysmal atrial fibrillation" European Heart Journal 1999;20:1429-1434
[22] Gillis AM, Connolly SJ, Dubuc M, Yee R, Lacomb P, Pilippon F, Kerr CR, Kimber S, Gardner MJ, Tang A, Molin F, Newman D and Abdollah H "Circadian variation of paroxysmal atrial fibrillation" American Journal of Cardiology 2001;87:794-798

Therefore the FDA could consider that **less than 30/84 or ≤35.7% (≤25.6%, ≤46.9%)** had reached the target level of decrease in transtelephonic transmissions.

3. 9 UNBLINDED QUALITY OF LIFE (QOL) QUESTIONNAIRE RESULTS

The QOL questionnaires used in this study, as a secondary endpoint, were the SF-36 and the AFSS. The results include patients that had AV node ablation and pacemaker implantations, previously shown to have an impact on QOL results.

SF-36 (scale goes from 0 to 100, with higher numbers better)
The baseline mean scores for all 8 domains of this instrument were lower than the norm.

SF-36 scores

SF-36 scale	General US population	Baseline patients n=81-83	Six month n=78-80
Physical functioning	84.2 ± 23.3	71.5 ± 25.8	77.2±25.2
Role physical	80.9 ± 34	42.1±43.5	59.4±44
Role emotional	81.3 ± 33	66.7±39.5	81.0±36.1
Bodily pain	75.2 ± 23.7	70.7±24.1	79.7±22.3
General health	71.9 ±20.3	63.0±21.2	63.4±10.5
Vitality	60.9 ± 20.9	47.3±22.3	58.7±20.9
Social functioning	83.3 ±22.7	71.1±26.5	83.0±21.4
Mental health	74.7 ± 18.1	74.9±16.0	78.9±15.5

Table 58. 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 (AFSS)
This is a disease specific quality of life scale. Cardima has changed the original ranges of the three portions of the scale (frequency at 11 points, duration at 8 points and severity at 10 points) to 100 point scales to make them similar to the SF-36 scales. 100 is the best possible and 0 the worst. They report the total AFSS score as the sum of the original three scale values transformed to a 100 point scale value.

Table 59. 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 do not answer some questions as they were not applicable.

Table 60. 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

Quality of life questionnaires are a relatively recent addition to clinical trials for atrial fibrillation. Gerstenfeld[23] et al has reported a single center study in which 71 patients underwent a left atrial ablation procedure or just a mapping procedure. These patients were given questionnaires one month before and 6 months after the procedure. Patients who only had the mapping procedure improved in only one QOL score. The patients who had the ablation procedure but who subsequently had recurrence of their atrial fibrillation improved significantly in all QOL measures. The patients who had a long term successful ablation procedure also improved in all QOL measures. The patients with long term sinus rhythm had greater improvement in two of the six QOL scores measured in that study.

The FDA has concerns about interpreting QOL results in patients who are unblinded especially in studies that do not have a control group. It is impossible to determine the extent of placebo effect in improving perception of symptoms without the patient being blinded to procedure.

3.10 SAFETY

This memo reports on all the adverse events that occurred in both phase IIb and III of the study. There were 131 patients who received the ablation procedure. All 131 received treatment with the Revelation Tx catheter, 77 with the NavAblator and 46 with a non-investigational catheter.

There were 5 patients who were identified as having a serious adverse event. In addition there were 4 patients that required implantation of permanent pacemaker shortly after the procedure, two within one or two days of the procedure and the others in less than two weeks of the procedure. If the 4 patients who received a pacemaker implantation shortly after the procedure are determined to be serious adverse events, the adverse event rate would be 9/131, or 6.9% (3.2%, 12.6%).

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[23] Gerstenfeld EP, Guerra P, Sparks PB, Hattori K, Lesh MD "Clinical Outcome after Radiofrequency Catheter Ablation of Focal Atrial Fibrillation Triggers" J Cardiovasc Electrophysiol 12:900-908, August 2001

Patient	Date of procedure	Date of adverse event	Adverse event within 7 days of procedure
III 53yo♂ no structural heart disease	10/24/01	10/24/01	Sinus node damage – asystolic pauses as long as 8.28 seconds documented 4 days post procedure. Medtronic Gem III AT implanted 11/1/01. Investigators thought sinus node dysfunction occurred during procedure. Also occurring in this patient: Aspiration pneumonia, Pericarditis without significant effusion , Posterior thoracic skin burns from defibrillation
III 66yo♀ nl echo	1/10/02	1/10/02	Tamponade requiring pericardial window – two hours post procedure became hemodynamically unstable. Hospitalized 11 days post procedure
III 5 ♀ hx hypertension and breast CA	4/27/01	4/27/01	Left femoral AV fistula requiring operative repair - procedure was 5hrs 45 minutes in duration, patient had 3 7F sheaths in left femoral vein and one 5F in left femoral artery. Initial palliative treatment failed and patient re-admitted one week post ablation for repair.
IIb 59yo♂ no structural heart disease	4/1/00	4/1/00	Sinus node dysfunction – Linear ablation procedure performed in atrial fibrillation. Failed cardioversion attempts x 6. Spontaneous termination of a fib several hours post ablation and was then in profound sinus bradycardia, requiring trancutaneous/temporary pacing. DDD pacer implanted 4/4/01.
IIb 48 yo♂	2/4/00	2/4/00	Left parietal embolic stroke – patient known to have protein C deficiency, history of pulmonary embolus, on coumadin prior to RFA. Procedure 898 5.5 hours in duration, catheter may have crossed atrial septum

Other patients requiring pacemaker implantation within two weeks of ablation procedure:

- ⚠ IIb – RFA procedure 7/6/99, pacemaker implantation 7/19/99
- ⚠ IIb – RFA procedure 3/22/00, pacemaker implantation 3/24/00
- ⚠ III – RFA procedure 12/3/01, pacemaker implanted 12/4/01 because of abnormal sin ode recovery time
- ⚠ III – DDD pacemaker implanted 9 days post procedure and worsening of AF required AV node ablation at 12 months

Adverse event greater than one week post procedure –

- IIb 1005 – ablation procedure on 6/6/00, embolic left middle cerebral artery stroke on 7/12/00. The patient had known pre-existing bilateral atherosclerotic carotid disease, but the pre-procedure TEE showed a small blood clot not reported at time of the TEE

There was one death. Pt IIb 308 had the right atrial linear ablation procedure on 4/26/00. He was diagnosed to have lung cancer 6/28/01, 17 months post ablation procedure. He was treated with chemotherapy and radiation. He died 9/13/01.

All complications possibly or probably related to procedure or device (from original PMA submission and A6, both phases IIb and III)

	Adverse event	days post ablation procedure	number of events
1	arrhythmias possibly requiring drugs and/or electrical cardioversion (no other description)	0-347	7
2	sinus/asystolic pauses	1-7	2
3	sinus node block requiring pacemaker	4	1
4	atrial fibrillation requiring hospitalization	4-251	4
5	supraventricular tachycardia	9-104	2
6	atrial flutter	25	1
7	increased palpitations	1	1
8	bleeding	0-3	3
9	cardiac perforation with tamponade	0	1
10	pericarditis	1	2
11	atypical chest pain	1	1
12	pneumonia	2	1
13	femoral arteriovenous fistula	1	1
14	deep vein thrombosis	9	1
15	nerve damage	1	1
16	infection	1-6	3
17	skin burn, rash, other dermatologic	0-6	6
18	pulmonary hypertension	167	1
19	other*	0-65	17
	total		**56**

*sore throat, back pain, generalized discomfort, feeling cold, weakness, groin ecchymosis, swollen lip)

Pacemaker implantation (± AV node ablation)

There were a total of 27 patients who had a pacemaker implanted during the course of the study, 14 of whom also had an AV node ablation. The rate of pacemaker implantation is 27/131 or 20.6%.

While the FDA agrees that this group of patients is at increased risk for conduction system disease this rate of pacemaker implantation is much higher than the literature reported rate of 4% to 8.6%.[24,25,26]

[24] Humphries KH, et al "New onset atrial fibrillation; sex differences in presentation, treatment and outcome" Circulation 2001;103:2365-2370

[25] Patton KK, Zacks ES, Chang JY, Shea MA, Ruskin JN, Macrae CA and Ellinor PT "Clinical subtypes of Lone atrial fibrillation" PACE 2005;28:630-638

[26] Nieuwlaat R, et al. "Atrial fibrillation management: a prospective survey in ESC member countries" European Heart Journal 2005;26:2422-2434

Listing of Study Subjects who had PPM Implants
during the Course of the Study
(Shaded if AV node ablation)

Phase	Subject ID	Ablation Date	AVN Ablation	Date of Implant	Comments
IIb		05/04/99	N	8/15/00	Subject had pre-existing Hx of SSS, brady-tachy syndrome
IIb		04/26/00	N	5/3/01	Subject had pre-existing Hx of SSS, junctional, brady and AF, mild HIS-Purkinje conduction disease.
IIb		03/23/99	Y	5/3/99	Subject had pre-existing Hx of SSS, pt requested AVN ablation and PPM.
IIb		05/27/99	Y	6/9/00	AV block started >1 year post Tx from AV blocking AADs AVN ablation and DDD pacer implanted.
IIb		04/03/00	N	4/4/00	Subject had pre-existing sinus block.
IIb		11/19/99	N	5/25/00	Pacer implanted after 6 months for tachy/brady syndrome.
IIb		03/22/00	N	3/24/00	Subject had pre-existing SSS with pauses.
IIb		04/30/99	Y	unknown	AVN ablation/PPM insertion for AF w/ RVR
IIb		06/03/99	Y	unknown	AVN ablation/PPM insertion for AF w/ RVR
IIb		07/06/99	N	7/16/99	Subject had pre-existing sinus pauses.
IIb		08/25/00	unknown	2/13/02	**1.5 years post procedure, atrial tachycardia required atrial defibrillator for resolution.**
III		06/21/01	?	08/21/02	**atrial ICD for persistent atrial fib post 12 mos FU visit**
III		08/29/01	N	1/10/02	PPM implanted for tachy-brady syndrome w/pauses of 2 seconds
III			Y		AVN/PPM 656 days post ablation for recurrent AF, not controlled
III		10/24/01	N	11/1/01	Gem III AT implantation required for sinus node damage from ablation procedure and continued AF.
III			Y		AVN ablation + DDD pacer for progressive AF, did not transmit 6 month TTM
III		09/21/01	N	1/28/02	DDDR pacer implanted for AV block w/non-sustained VT seen on Holter at 3 months.

Phase	Subject ID	Ablation Date	AVN Ablation	Date of Implant	Comments
III		7/16/01	Y	11/5/01	Patient had insurance change and therefore changed physicians. AVN ablation/PPM performed at that time.
III		12/03/01	N	12/4/01	Had PPM implanted for abnormal sinus node recovery times and pauses up to 3 seconds from a pre-existing condition SSS.
III			Y		AVN/PM at 8 months post ablation for chronic AF
III		04/05/01	Y	12/12/01	AVN w/PPM eight months after the procedure.
III		07/19/01	Y	1/3/02	PPM implanted 1/3/02. No AF before pacer insert was reported, however, AVN ablation was performed prior to PPM.
III			Y		AVN/pacer for recurrent AF 190 days post ablation
III		02/14/02	Y	5/6/02	developed atrial flutter, then persistent AF, had AVN ablation with VVIR pacer at 3 months
III			Y		recurrent AF, not controlled, AVN/DDDR 67 days post ablation
III			N		DDD implanted 69 days post ablation, continued AF after ablation
III			Y		DDD PPM placed 9 days post procedure, worsening of AF required AV node ablation at 12 months

3.16 LONG TERM FOLLOW UP

Sixty four phase III patients have completed 12 month follow up and 30 have completed 24 month follow up as of the Amendment 6 submission.

Of the 64 patient with 12 month follow up there have been 5 hospitalizations for AF, 5/64 or 7.8% and of the 30 with 24 month follow up there have been 7 hospitalizations for AF or 7/30, 30%.

Five patients have had ablation procedures, other than AV node ablations; 2 pulmonary vein isolation procedures, 1 pulmonary vein isolation plus atrial flutter and one repeat right atrial “linear” ablation procedure.

Table 86. AAD medication use at baseline and in follow-up.

		Visit Type							
		Baseline (N=93)		6 Month (N=88)		12 Month (N=64)		24 Month (N=30)	
		Freq	%	Freq	%	Freq	%	Freq	%
AAD Class	Medication								
Amiodarone	Amiodarone	18	19.4	15	17.0	11	17.2	3	10.0
Membrane Active	Disopyramide	4	4.3	2	2.3	2	3.1	1	3.3
	Dofetilide	8	8.6	7	8.0	6	9.4	4	13.3
	Flecainide	8	8.6	18	20.5	12	18.8	2	6.7
	Propafenone	11	11.8	5	5.7	5	7.8	1	3.3
	Sotalol	20	21.5	12	13.6	8	12.5	4	13.3
Rate Control	Atenolol	13	14.0	15	17.0	11	17.2	7	23.3
	Carvedilol	1	1.1	1	1.1	1	1.6	-	-
	Digoxin	12	12.9	8	9.1	6	9.4	5	16.7
	Diltiazem	19	20.4	11	12.5	5	7.8	-	-
	Metoprolol	12	12.9	16	18.2	12	18.8	7	23.3
	Propranolol	3	3.2	2	2.3	3	4.7	1	3.3
	Verapamil	5	5.4	4	4.5	2	3.1	-	-

Freq = frequency

Section 4. Reasons for Not Approvable determination

Based on a review of the PMA and relevant amendments, FDA has determined that the Revelation Tx catheter system remains NOT APPROVABLE due to the inability to adequately assess the device's effectiveness and risk-benefit safety profile. The primary reasons for the NOT APPROVABLE determination are:

Procedural effectiveness data for the Revelation Tx catheter was not collected as was dictated per the investigational protocol. It can not be objectively determined if any patient had an effective line of lesions performed.

It cannot be determined that any patient received the ablation treatment successfully. Any clinical success can not be attributed to the ablation procedure without knowing whether or not the patient actually had successful completion of the Cardima linear lesion set.

Also the FDA can not conclude that the individual ablation procedures were similarly conducted to allow the data to be pooled across investigational sites.

The study demonstrated that the NavAblator catheter was insufficiently effective at producing bidirectional conduction block at the cavotricuspid isthmus.

The effectiveness endpoint for the NavAblator catheter was demonstration of bidirectional conduction block at the cavo-tricuspid isthmus. The NavAblator catheter produced

bidirectional conduction block in 48/77 patients or 62.3%. The catheter performance did not reach the performance criterion of 90% (lower bound 80%).

The chronic clinical effectiveness endpoint measurement was not adequately assessed.

The baseline and six month transtelephonic transmission may not accurately count the number of atrial fibrillation episodes.

There was no method in place to determine if each transmission represented a discrete atrial fibrillation event. It is unknown if more than one transmission was sent or recorded per atrial fibrillation event.

There is inherent bias in the frequency of patient episode event reporting at baseline and at 6th month

The bias toward over reporting at baseline and under reporting at the sixth month would lead to an over optimistic assessment of the effectiveness of the device system yet only 30/84 or 35.7% (25.6%, 46.9%) could be classified as having the required number of decreases in telephone transmissions.

There is no method available to determine the extent of placebo effect on the self reported symptomatic atrial fibrillation episodes.

Quality of Life (QOL) questionnaires were completed by patients in this study. This data has to be viewed with skepticism as the study was unblinded and there was no comparison group. Also the QOL questionnaires were completed by all the patients including patients with AV node ablation procedures.

The risk-benefit profile is not able to be determined for the Cardima ablation catheter system.

Effectiveness is not able to be determined.

The 20.6% rate of pacemaker implantation seen in this group of relatively healthy patients with paroxysmal atrial fibrillation is concerning compared to the literature rate.

STATISTICAL REVIEW OF PMA

Date March 12, 2007

From Mathematical Statistician (Heng Li) HFZ-550
Division of Biostatistics, OSB

Subject Statistical Memo for Dispute Resolution Panel, Cardima, Inc.
REVELATION Tx Ablation System,

To Lisa Leveille - HFZ-450
Division of Cardiovascular Devices, ODE

This review covers PMA P020039/A6, and is essentially limited in scope to the evaluation of chronic effectiveness based on the primary clinical effectiveness endpoint (for chronic effectiveness). For the definition of this endpoint please refer to Section 2.2 of the clinical review memo. It seems to this reviewer that the clinical study as has been conducted does not provide an adequate amount of reliable information to make it possible to evaluate the chronic effectiveness of the investigational device system.

The measurement associated with the primary clinical effectiveness endpoint is based entirely on patient reporting of the number of baseline and six-month AF episodes. The patient-reported number of baseline AF episodes may be higher than the actual number of baseline AF episodes. In other words, there may be over-reporting of the number of AF episodes at the baseline. The patient-reported number of six-month AF episodes may be lower than the actual number of six-month AF episodes. In other words, there may be under-reporting of the number of AF episodes at the six-month follow-up. Examples of factors that may contribute to over-reporting at baseline include the desire to be enrolled in the study (a minimum number of AF episodes per month is required to be enrolled in the study) and the tendency to report one AF episode as multiple AF episodes (due to inexperience or intentionally in order to be enrolled in the study). Examples of factors that may contribute to under-reporting at six-month follow-up include lack of motivation and lack of compliance (for various reasons). The study was conducted in such a way that there were no operational procedures in place to satisfactorily contain the influence of those factors on the reporting of the number of AF episodes, and the extent to which over-reporting at the baseline and under-reporting at the six-month follow-up has affected the measurement associated with the primary clinical effectiveness endpoint cannot be usefully calibrated.

In addition to the measurement problem of over-reporting at the baseline and under-reporting at the six-month follow-up, which keeps the actual numbers of AF episodes from being observed, there are other challenges to the evaluation of chronic effectiveness. The primary clinical effectiveness endpoint as defined in the investigational plan involves

the comparison of the numbers of episodes (during a one month period) at baseline and six-month follow-up. Multiple factors other than the chronic effectiveness of the investigational device system contribute to the result of such a comparison. Examples include random fluctuation of monthly number of AF episodes over time for each patient, the selection of baseline period during which to report the number of AF episodes, medication and change in medication such as dose increase, and other artifacts (e.g., psychological) unrelated to the chronic effectiveness of the investigational device system.

Based on the information available to this reviewer and with the help of the clinical reviewer, the results on the primary clinical effectiveness endpoint for phase III patients can be summarized by the following table:

Success	Failure	Total
≤30	≥54	84
≤35.7%	≥64.3%	100%

In the above table 'Success' ('Failure') refers to that associated with the primary clinical effectiveness endpoint defined in the protocol (see clinical memo). The symbol '≤' means that based on the information available we know that at most 30 out of the 84 (i.e., 35.7%) Phase III patients can be called successes with regard to the primary clinical effectiveness endpoint. Given the above annotation, the symbol '≥' in the above table should be self-explanatory. Continuing to use the symbol '≤' to indicate 'at most,' a 95% confidence interval for the proportion of success can be expressed as (≤25.6%, ≤46.9%). It should be emphasized that the proportion 35.7% is a very optimistic point estimate (and likewise (25.6%, 46.9%) a very optimistic interval estimate), since it does not take into account any measurement problem of over-reporting at the baseline and under-reporting at six-months of the number of AF episodes, nor does it take into account the use of non-investigational catheters (patients in whom non-investigational catheters were used should be counted as failures but the id's of those patients are not available). It is very likely for 35.7% (and likewise the interval (25.6%, 46.9%)) to be a substantial over-estimate of the proportion of success associated with the primary clinical effectiveness endpoint.

The fundamental measurement and confounding problems discussed above make it impossible to draw any reasonable conclusions regarding the chronic effectiveness of the investigational device system (or any sub-system thereof). We do not have any information on the joint distribution of the numbers of baseline and six-month AF episodes (observed or actual) corresponding to a completely ineffective device (or sham procedure) investigated in a study designed and conducted in exactly the same way as the pivotal study, and therefore do not have any basis from a statistical perspective to be able to evaluate the chronic effectiveness of the investigational device system (or any sub-system thereof).

While there is a lack of reliable information on chronic effectiveness, the information on acute effectiveness is totally missing for the Revelation Tx catheter. Since Revelation Tx catheter is a major component of the investigational device system, it is essentially the case that there is 100% missing data regarding acute effectiveness for the investigational device system as a whole. Furthermore, it is worth pointing out that we cannot even be sure that each site actually used the same acute treatment protocol for the Revelation Tx

catheter, which raises the question of how analyses that pool data across investigational sites can be meaningful or interpretable. With regard to safety, 5 patients are known to have had a serious adverse event, and 4 patients received a pacemaker very shortly after the procedure (see the clinical memo for more detail).

One note that this reviewer would like to make concerns analyses that the sponsor carried out in which reported AF episodes (both at baseline and at six-month follow-up) less than a certain amount of time apart are counted as one episode. This analysis does not address the measurement problem of over-reporting at the baseline and under-reporting at the six-month follow-up, because in this analysis the reported number of AF episodes at six-month follow-up is replaced by a smaller number for some patients and is left unchanged for the rest of the patients. This analysis (referred to by the sponsor as a sensitivity analysis) does not address any confounding problems either.

In summary, it is this reviewer's impression that there do not seem to be any statistical methods that can be used in order to reach a conclusion regarding the chronic (or acute) effectiveness of the investigational device system (or any part of the system). This conclusion is largely due to the lack of rigor with which this study was actually conducted.