Section 7A: Excerpts of PMA submission

P020039 (original PMA):

1. Clinical review memo dated 10/23/2002
2. Statistical review memo dated 11/19/2002
3. Lead review memo dated 11/8/2002
4. Major deficiency letter dated 11/14/2002
5. Results section as submitted by Cardima: PMA Volume 7 pages 47-133
6. Representative CRFs as submitted by Cardima: PMA Volume 8 pages 88-98
7. Cardima animal study data

P020039/A002 (response to major deficiency letter):

8. Clinical review memo dated 6/23/2003
9. Statistical review memo dated 4/12/2003
10. Lead review memo dated 6/23/2003
11. Cardima response to FDA's deficiencies: PMA pages 1-38
12. Agenda for May 29, 2003 Advisory Panel Meeting
13. Not approvable letter dated 6/26/2003

P020039/A006 (response to not approvable letter):

14. Clinical review memo dated 3/20/2004
15. Statistical review memo dated 4/30/2004
16. Not approvable letter dated 5/21/2004
17. Cardima's response to FDA's 6/26/2003 letter: PMA pages 1-21
18. Results section as submitted by Cardima: PMA pages 65-142

CLINICAL REVIEW OF PMA

TO: CINDY DEMIAN, MS, BME

FROM: DR. LESLEY EWING

DATE: 23 OCTOBER 2002

SUBJECT: P020039

SPONSOR: CARDIMA, INC.

DEVICE: REVELATION® TX MICROCATHETER WITH NAVABLATOR ABLATION SYSTEM

CC: ELIAS MALLIS

Purpose of submission: This modular PMA intends to show that this ablation system is safe and effective for the treatment of drug refractory paroxysmal atrial fibrillation.

Materials reviewed: I have reviewed the clinical module, module 5. There are 5 volumes to module 5. They are numbered volume 7 – 11. Volume 7 contains background information, the summary of the clinical study, draft SSED and draft labeling. Volumes 8, 9 and 10 contain the Case Report Forms on patients [redacted] Volume 11 contains the journal articles from the bibliography.

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."

Device description:

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 electrodes and eight thermocouples in a linear array near the distal end of the catheter. The ablation electrodes are 6mm in length. Radiofrequency energy is applied to each electrode individually. The catheter is meant 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.

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. The sponsor states that "The NavAblator is intended for the creation of lesions (either linear or focal) from its tip when diverse myocardial anatomy requires the features of a "hot tip" ablation catheter to achieve effective lesions." (Volume 7, page ii)

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 has been cleared under K974683.

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

Supportive data:

Animal studies (pre-clinical studies summary from module 5):

Volume 7, page iv "the Revelation Tx was capably of creating continuous, linear transmural lesions, that a continuous lesion can be formed from sequential electrode ablations; 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."

Clinical study:

The premarket application is supported by a clinical study conducted under the IDE G970280. The study began in December 1997. It is a multi-center, prospective, non-randomized single arm study. The study was conducted in three phases with three different study endpoints and study protocols. These phases were Feasibility or phase IIa (n=10 pts), Expanded Feasibility or phase IIb (n=38 pts) and Pivotal or phase III (n=61 pts). The pivotal phase is ongoing. There were 3, 15, and 20 sites involved respectively. The sponsor states that the 99 patients of the Expanded Feasibility and Pivotal phases are the data meant to support the market application, but 4 patients do not have monitored data available.

The protocol, page 209, states that the sample size will be 80 completed subjects for the Phase III study.

The study had a DSMB. The DSMB met three times, twice by teleconference to review the study. The DSMB included a biostatistician, an electrophysiologist and a cardiologist.

Summary of protocol, phase III pivotal

Procedural endpoint:
There was a procedural endpoint listed for both phase IIa and IIb. There are multiple descriptions of this procedural endpoint. From page 42 the procedural endpoint is described as "a reduction in post-ablation amplitudes relative to pre-ablation." This was to be measured by "demonstration at the lines of ablation during sinus rhythm at least one of the following: a) reduction in the amplitude, fragmentation or widening of local electrograms or b) split potentials. From protocol page 207, volume 7, "The procedural endpoint of this study is electrogram amplitudes post-ablation relative to pre-ablation." From page 72, "The protocol defines procedural (acute) success as a reduction in electrogram amplitudes at the line(s) of ablation post-ablation compared to pre-ablation. Three

21

indicators represent such changes: a) reduction in the amplitude, fragmentation or widening of local electrograms; b) the appearance of split potentials; or, c) an increase in pacing thresholds."

The requirement to measure electrogram amplitude pre and post ablation was removed for Phase III (S7, August 3, 1998). 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".

Primary effectiveness endpoint: Reduction in frequency of symptomatic episodes during the 6th month of follow-up compared to the baseline frequency. 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.

Page 210 of 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. No threshold was included in the protocol.

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

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 feel the 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 a fib in the baseline period. Patients were not told the number of episodes required to be considered for ablation.

Patients who fail the initial screening are allowed to rescreen. They are then required to have 9 total episodes in 90 days, which would average to be 3 per month.

22

Baseline testing: history and physical, PT/PTT & INR, "stress test", ECG and QOL questionnaires. These questionnaires are the SF-36 and the Atrial Fibrillation Severity Scale (AFSS).

TEE was to be performed within 48 hours of the ablation procedure.

Procedure

During procedure all patients are heparinized with ACT maintained at 200 – 300 seconds.

Before ablation the investigator is to record bipolar electrical signals to determine good tissue contact. "In general, sharp electrograms with high frequency components and large relative amplitudes indicate good contact." Then pacing thresholds are to be measured while patient is in sinus rhythm. "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."

A pacing protocol is provided to locate the position of the phrenic nerve.

From protocol "Apply RF along three trajectories (posterolateral, posteroseptal and along the isthmus) a fourth trajectory (anterior) may be included at the option of the investigator." All three linear lesions are to be produced with the Revelation Tx. "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 protocol also states that "conduction block may be verified using coronary sinus pacing while recording with a multipolar catheter deployed in the right atrium." And the protocol goes on to states "If bi-directional conduction block cannot be obtained with the above procedure, the physician should complete the isthmus trajectory using standard institutional procedures."

The RF energy is delivered to one of the eight electrodes at a time.

The investigator was instructed to measure bipolar electrograms and pacing thresholds "to assess changes that have occurred as a result of the RF energy application."

Follow-up Assessments Post Ablation

Assessment	1 month	3 month	6 month	12 month	24 month
Exam/history	X	X	X	X	
Review event recordings	X	X	X		
Review of adverse events	X	X	X	X	X
Review of prescribed medications	X	X	X	X	X
Review of hospitalizations or ER visits	X	X	X	X	
Arrhythmia review	X	X	X	X	
NYHA class	X	X	X	X	
ECG	X	X	X		
PT & INR	X	X			
Stress Test		X			
TTE		X			
Quality of Life Questionnaires		X	X		

23

Per page 77 of submission, "Weekly event monitor transmissions are compulsory during month one, month three and month six, even if the subject does not experience symptomatic episodes."

Some differences between the Expanded Feasibility phase (IIb) protocol and the Pivotal phase (III) protocol are:

- In Phase III there was the addition of the NavAblator catheter or *a 4mm ablation catheter of the investigators choice* to complete the linear lesions thought to be required to treat atrial fibrillation

- There seems to have been a different procedural endpoint for all three phases. The requirement to measure electrogram amplitude pre and post ablation was removed for Phase III (S7, August 3, 1998). 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".

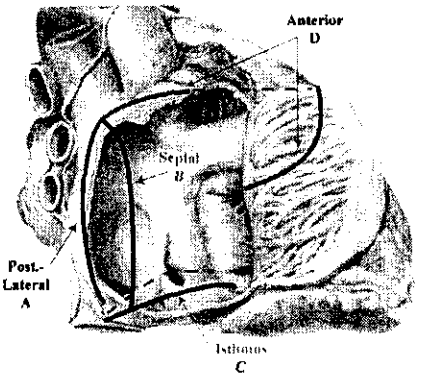
- The primary objective in phase IIb was to prove the effectiveness of the Revelation Tx to create the linear lesions that would treat atrial fibrillation and in phase III the objective was to determine if the procedure was effective to decrease atrial fibrillation episodes.

After enrollment, before ablation, the patients are monitored for 30 days and must have at least three documented symptomatic atrial fibrillation (AF) episodes within the monitoring period in addition to the other inclusion/exclusion criteria. . There were 5 patients whose screening rhythm strips were disputed when reviewed by cardiologists but they had already been ablated at that point. Their data is included in the submission despite their baseline AF episode frequency being unknown.

Follow-up was for 24 months which included visits at 1, 3, 6, and 12 months and a telephone interview at 24 months. Stress testing at 3 months post-ablation is included in the protocol but results are not reported and analysis of results was never included in the plan of the study.

Ablation procedure actually performed:

Four linear lesions in the right atrium were part of the ablation protocol, but not all patients received all these lesions. The locations of the lesions were: postero-lateral (A), septal (B), tricuspid isthmus (C) and anterior (D).



From Table F-45, "Lesion Lines Ablated during RF ablation Treatment"
Page 126

Lesion lines	Number of patients	%
ABC	78	82.1
AB	6	6.3
ACD	5	5.2
AC	2	2.1
ABCD	2	2.1
BC	1	1.1
BCD	1	1.1
Total	**95**	**100**

The Revelation Tx catheter was used to create all lesions A, B and D. The tricuspid isthmus lesion or C was not able to be created with the Revelation Tx in all patients. Some patients required the NavAblator or some other 4mm tip ablation catheter used off-label.

Catheters used to make lesion C (from Table F-46, page 128)

Catheters	Number patients (total that had lesion C = 89)	%
NavAblator only	34	38.2
Revelation Tx only	20	22.5
Other only	18	20
Revelation Tx, other	10	11.2
NavAblator, other	5	5.6
Revelation Tx, NavAblator	2	2.2

The number of patients that were treated with only the investigational catheter system is 56. It is not known from the submission which lesion set these 56 patients had during their

ablation procedure, or any other characteristic of these 56 patients such as how long was their follow-up.

"Other" catheters used were: (from table F-47, page 128)

- Blazer n = 16
- Navistar n = 7
- Medtronic n = 6
- Chilli n = 3

Total n=32

At least one third of the patients in this study required treatment with a non-investigational catheter because the investigational device failed to produce the lesion required.

The total number of patients that were treated with "other" catheters from Table F-46 is 33, and the total from Table F-47 is 32. The sponsor does not provide the outcome of the procedure for the patients that were treated with another device besides the investigational catheter. The only data provided on the effectiveness data combines all patients, regardless of which procedure they received or with which device they were treated.

The indication for use statement is "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."

It is unclear to me how the patients who had a different procedure performed in the clinical study provide evidence to support the procedure in the indications statement. 78 patients had the procedure performed in the clinical study as what will be indicated if the device is approved. It is unclear from the submission how many of those 78 patients had at least 6 months follow-up.

The sponsor does not discuss why they feel the data from the patients treated with a non-investigational device should be included with the effectiveness data and not considered failures of the investigational device system. Section 7.8, page 121, provides a brief cursory discussion of pooling of the different phases of the study and the different lesion sets and different ablation catheters. This discussion is not sufficient to answer the questions raised by this clinical trial.

Summary of study results:

99 patients ablated under phases IIb and III, but only 95 have monitored data
80 have at least 6 months follow-up, but effectiveness data available only for 79 patients at 6 months
53 have at least 12 months follow-up
29 have 24 months follow-up

The follow-up of the 78 patients who received the most common 3 linear lesion set (posterolateral, septal and tricuspid isthmus) during their ablation is not specified.

3/95 patients had a second ablation procedure with the Revelation Tx, so there are 98 procedures in 95 patients.

Demographics:

72/95 male, 75.8% ages of men 35.3 to 75.9, mean was 56.4 ± 10.21.2002
23/95 female, 24.2 age range of women 27.9 to 77.1, mean was 62 ± 10.7
Overall mean age 57.8 ± 10.6
74.7% of the patients had concomitant heart disease

Withdrawals:

7 patients withdrew from the study prior to 6 months follow-up
11 patients total have withdrawn after ablation procedure performed, 6 of whom had pacemakers implanted and 2 had a MAZE procedure

Protocol Deviations:

There were 56 protocol deviations (page 44) which mainly consist of laboratory/assessments not performed. There were an additional 20 "Allowable Deviations" (page 45). It appears that these were "allowable" because of some patient condition. But included in this list are three patient not in sinus rhythm at time of the procedure. The submission states that the patients went back into atrial fibrillation after cardioversion. **These patients would not be classified as having paroxysmal atrial fibrillation if they were not able to be cardioverted. Also it is unclear how the acute procedural endpoint of these patients was determined. More information is needed on patients**

Procedural data

Table F-43, page 111 reports 22 procedures in which there were catheter performance problems, 3 procedures in which there were problems with the Tx Select Switchbox, and three procedures in which there were problems with the NavAblator catheter..

Acute procedure success

The requirement to measure atrial amplitude change after ablation was removed in Phase III. The sponsor report amplitude reduction in 52 procedures for the posteroseptal and posterolateral lines, 16 procedures for the isthmus line and 2 procedures for the anterior line. They discuss the difficulties in this particular measurement because of catheter movement.

The discussion of acute procedural endpoints in the submission mentions that bi-directional block at the isthmus line is the success endpoint for that portion of the study. They do not report any data on bi-directional block. The measurement of bi-directional block is not included in the study protocol.

It is unclear to me how the physician doing the study knows when he or she has completed the ablation.

Baseline episode frequency

Baseline number of symptomatic atrial fibrillation episodes

Number of episodes	Number of patients	% of total 95
3	14	14.7
4	15	15.8
5	7	7.4
6	9	9.5
7	4	4.2
8	6	6.3
9	9	9.5
10-14	16	16.8
15-19	5	5.1
20-29	6	6.1
30+	4	4.2

The sponsor states the mean of the above data, as 9.9 ± 9.1, and the median is 7.0 **I don't think that the mean or median of all this data is clinically significant. What is important is the amount of change each patient does or does not make after ablation. It is interesting that the frequency of episodes seems to group around 3-4 episodes per month (30.5%) and 10-19 episodes per month (21.9%). Is this bimodal distribution significant?**

AF episode frequency reduction:

Baseline AF frequency was a mean of 9.9 ± 9.1 episodes. The overall frequency for 79 patients at 6 months is reported to be 1.9 ± 2.9. 57/79 (72.2%) patients at six months had fewer than three episodes per month. It appears from table F-29a that 37 out of 79 (46.8%) patients had no symptomatic AF episodes at 6 months follow-up.

Percent reduction in arrhythmia episodes *(from sponsor's table f-29a, page 82)*

Frequency of AF episode and episode reduction	**6 month follow-up n=79**
# subjects with episode reduction	72/79 (91.1%)
≥50% reduction	67/79 (84.8)
100% reduction	37/79 (46.8)
<50% reduction	12/79 (15.2)
Withdrew	7
Non-compliant with event recorder	1
Mean % reduction ± SE	74.7 ± 4.9

There were 5 patients whose baseline frequency was disputed and these patients are included in the above data.

The sponsors do not present the data according to the change occurring per patient. They present the numbers of patients who had certain numbers of episodes at baseline and at six months but it cannot be known from the data what happened to each group of patients. The patient who had 3 episodes at baseline might be one of the patients who had 10 episodes at 6 months.

The above data does suggest that this group of procedures, with several different devices, has made symptom load decrease. <u>It cannot be discerned though which procedure, lesion set or catheter was effective.</u>

From Table F-30, Change in antiarrhythmic drug use from baseline to six months (n=80)
(Page 85)

Change	Patient number	Percent
Decrease	33	41.3
No change	26	32.5
Increase	21	26.2

It is not stated whether there were patients who were able to come off medications.

<u>Quality of Life results</u>
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.

Baseline SF-36 scores

SF-36 scale	General US population	Study patients N=87-91*
Physical functioning	84.2 ± 23.3	71.5 ± 2.7
Role physical	80.9 ± 34	38.5 ± 4.5
Role emotional	81.3 ± 33	64.8 ±4.2
Bodily pain	75.2 ± 23.7	69.0 ±2.5
General health	71.9 ±20.3	60.7 ±2.3
Vitality	60.9 ± 20.9	44.5 ±2.3
Social functioning	83.3 ±22.7	70.7 ±2.8
Mental health	74.7 ± 18.1	73.0 ± 1.9

***5 patients did not complete the questionnaire at baseline and not all patients answered all questions**

Baseline and Follow-up SF-36
Mean ± SE

SF-36 scale	Baseline N=86-90*	Three month N=75-78*		Six month N=71-75*	
Physical functioning	71.5 ± 2.7	78.3 ± 2.7	<0.001	79.4 ± 2.7	
Role physical	38.5 ± 4.5	60.7 ± 4.9	<0.0001	58.8 ± 4.9	<0.0001
Role emotional	64.8 ±4.2	77.3 ± 4.0	<0.05	74.9 ± 4.6	0.06
Bodily pain	69.0 ±2.5	75.7 ± 2.8	<0.01	76.1 ± 2.9	
General health	60.7 ±2.3	61.8 ± 2.3		61.2 ± 2.4	
Vitality	44.5 ±2.3	55.3 ± 2.5	<0.0001	54.7 ± 2.7	<0.0001
Social functioning	70.7 ±2.8	79.7 ± 2.8	<0.001	82.1 ± 2.7	<0.001
Mental health	73.0 ± 1.9	76.7 ± 1.8		76.4 ± 2.0	

* Range of response sample size for each of the eight domains

Atrial Fibrillation Severity Scale (AFSS)
This is a disease specific quality of life scale. The sponsor 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.

Baseline and Follow-up AFSS scores
Mean ± SE

	Baseline N=88-89*	Three month N=66-72*		Six month N=60-71*	
Episode frequency	30.1 ±2	45.4 ± 3	<0.001	49.7 ± 3.2	<0.001
Episode duration	38.0 ±2.6	49.0 ± 3.7	<0.001	49.8 ± 4.3	<0.01
Episode severity	49.1 ± 2.6	66.9 ± 3.1	<0.001	67.1 ± 3.4	<0.001
Total AFSS	36.0 ± 1.5	47.8 ± 2.1	<0.001	50.8 ± 2.4	<0.001

* Range of response sample size for each of the four domains

The sponsor does not report the number of patients who had a clinically significant change in their QOL scores. The sponsor does not describe the method of administering the questionnaires. The sponsor does not address how to correct for placebo effect in this single arm unblinded study.

Adverse events

There were 57 adverse events total reported to the sponsors. This number includes adverse events that occurred after 7 days post-procedure. It appears that the sponsor is using a narrow interpretation of the standard adverse event definition included in their protocol. They have

included an alphabetical listing of all adverse events reported by the investigators but have included details on a selection of patients who had adverse events.

The sponsor states that there were 4 major adverse events in 4 patients.

1. perforation and pericardial effusion in patien
2. SA node dysfunction in patient
3. stroke in patient
4. AV fistula requiring surgery in patient

In my initial review of the list of all adverse events I have found additional events that possibly fit the adverse event definition in the protocol. More information is required to make the determination.

1. SA node dysfunction, bradycardia requiring pacemaker implantation in patient (required information may be in the submission)
2. arrhythmia exacerbation requiring cardioversion in patient
3. defibrillation burns patients
4. drug reaction (?) patient
5. AV fistula patient
6. hematoma patient
7. infection patient
8. infection patient
9. nerve damage patient
10. pericarditis in patients
11. pneumonia in patient
12. skin burns patient (information may be in the submission)
13. hematoma patient
14. SA node dysfunction patient
15. sore throat and URI patien
16. SVT patient

As all the ablation lesions were placed in the right atrium the safety profile of this procedure should be comparable to an SVT ablation procedure. The patient population is probably older and would have more co-morbidity. The OPCs for SVT ablation studies requires the major adverse event to be less than 7% upper 95% confidence limit. If the above additional 14 patients are added to the adverse event list the rate of adverse events would be 18/95 patients or 19%.

Conclusion:

This study has many serious flaws. I think that the data is uninterpretable.

Deficiencies:

1. You have submitted a premarket application for an ablation system that includes two ablation catheters. In your supporting clinical trial one catheter, the Revelation Tx was tested in 95 patients and you have provided 6 month follow-up on 79 of those patients. The other catheter, the NavAblator was tested in 41 patients. In five of these patients, another non-investigational ablation catheter from another manufacturer used off-label was required to complete the procedure. The FDA is concerned that the amount of clinical testing you have provided for the NavAblator does not provide a reasonable assurance of safety and effectiveness for this device. Please provide more clinical data for this

device or alternatively provide justification for why you think that this amount of clinical testing does provide adequate clinical testing.

2. You have provided summaries of follow-up and outcome for the patients involved in the clinical trial. The FDA review team requires more information of the patients to thoroughly review your application. Please provide a table of all patients who have been ablated with your ablation system which includes the patient identifier, date of procedure, catheters used and numbers(amount) of each, follow-up completed and dates, baseline atrial fibrillation rate, atrial fibrillation rate at 6 months, medications at baseline and at the 6 month assessment.

3. You have provided a summary of patient atrial fibrillation episode reduction in terms of amount of patients who had certain frequencies of events at six months. Please provide a complete tracking of the change in event frequency per patient or patient group. For example your study included 14 patients who had 3 events per month at baseline, what was the status of these 14 patients at the 6 month follow-up. This data would necessitate the removal of the 5 patients who did not have an accurate baseline frequency recorded. Please provide the identifiers of those 5 patients.

4. You have provided summary adverse event information for your clinical trial. In order to perform a complete review of the study the FDA review team requires additional information on patients [redacted] Please provide a summary of the adverse events that occurred and provide all the data monitoring forms and any other information, such as discharge summaries, used for your assessment of these adverse events.

5. You have provided summary data for all the patients treated with your ablation system and this includes patients who have been treated with non-investigational ablation devices, including a cooled ablation catheter. Please provide justification, both clinical and statistical, for pooling this data. This justification should include the effectiveness data assessment for the patients who were treated only with the investigational device. Please justify why the patients who required treatment with a non-investigational device should not be treated as failures of your device system.

6. Your clinical trial includes many variables, such as many different devices, different ablation procedures performed, and different study protocols for different phases of the investigation. Please provide a statistical justification for pooling of the data generated by the trial.

7. The secondary effectiveness endpoint of your clinical trial was improvement in quality of life as measured by two instruments, the SF-36 and the Atrial Fibrillation Severity Scale, compared to baseline measurements. You have provided the mean scores and standard error for baseline, three month and six

month follow-up. Please provide the number of patients who achieved a clinically significant improvement or worsening from baseline to the six month follow-up. Please provide the details of how the QOL questionnaires were administered. Also please address adjusting for placebo effect in this single arm unblinded clinical trial.

8. The acute procedural endpoint was dropped from the clinical trial protocol between phases IIb and III. Please explain how the investigators in phase III determined when they had produced effective lesions. Is it your intention that the ablation procedure would be strictly anatomically based? Are you intending to recommend measurement of bi-directional block to assess the adequacy of the tricuspid isthmus ablation line?

9. The primary effectiveness endpoint of the trial was decrease in frequency of atrial fibrillation episodes from baseline to 6 months follow-up. This was assessed by transtelephonic event recordings which were described as "mandatory" weekly in month three and six. This is not described in the investigational protocol. Please provide an assessment of compliance with the transtelephonic recordings per patient. Was there any other method in place to determine if patients were having symptoms not reported?

10. Please provide details of the baseline monitoring period per patient. This should include number of recorded events and their electrocardiographic diagnosis, such as sinus tachycardia, atrial fibrillation, etc. Please add the calculation of the percentage of recordings per patient that were diagnosed to be atrial fibrillation.

11. In the initial review of your clinical summary in your PMA submission it appears that you have included the 11 patients who withdrew from the study after having an ablation procedure in your assessment of effectiveness. Please provide a justification for this approach, especially for the 6 patients who subsequently were treated with a pacemaker and the 2 who had a MAZE procedure after the ablation procedure. Please provide the identifier numbers for these patients and the details of their treatment in your effectiveness assessment.

12. You have provided a list of all the adverse events reported by the investigators arrange alphabetically by adverse event. Please provide a list of adverse events grouped by patient.

13. Table F-18, page 64 of your submission, shows the baseline number of symptomatic atrial fibrillation episodes that occurred in the patient population of your study. It appears that there may be two groups of patients, grouped around 3-4 episodes per month and again at 10-19 episodes per month. The FDA is concerned that bimodal distribution may represent a significant different in groups of patients. Please justify the pooling of all these patients.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date November 19, 2002

From Mathematical Statistician (G. Kamer) HFZ-542
Division of Biostatistics, OSB

Subject Statistical Review of PMA P020039; REVELATION Tx Ablation System, Cardima, Inc.

To Cindy Demian – HFZ-450
Division of Cardiovascular Devices, ODE
Through: Director, Division of Biostatistics, OSB SC

INTRODUCTION

The Cardima REVELATION Tx Microcatheter 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 "hot tip" ablation catheter (8F) with an electrically active tip. This system is indicated for 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 in the right atrium.

The study design is a multi-center (20 enrolling centers), prospective, non-randomized, single-arm, controlled study in which patients serve as their own control. The control is the establishment of a baseline for each patient during a monitoring period in which patients record symptomatic episodes of AF with portable event monitor cards and transmit these recordings once per week during a 30-day period prior to final determination of eligibility and subsequent treatment.

The purpose of this study is to assess the safety and effectiveness of the REVELATION System in the treatment of patients with drug refractory paroxysmal AF by creating linear lesions with RF energy in the right atrium. The primary effectiveness endpoint is the frequency of any spontaneous symptomatic episodes of AF experienced by the patient. Quality of Life is a secondary effectiveness endpoint. Quality of Life is measured by the Medical Outcomes Trust Short Form 36 (SF-36) and the Atrial Fibrillation Severity Scale (AFSS). The incidence of complications is the primary safety endpoint.

STATISTICIAN'S COMMENTS

It is important to state that both clinical and statistical checklist processes suggested that this PMA not be filed at this time due to insufficient detail to permit meaningful in-depth reviews. While this in-depth statistical review will attempt to establish deficiencies to be addressed by the sponsor, the lack of detail in this PMA submission may lead to the identification of additional deficiencies as details are provided to replace generalities.

The following are statistical deficiencies which exist in this submission and may be forwarded to the sponsor for response:

1. Please provide statistical and clinical justification for the pooling of the data from the Expanded Feasibility and Pivotal studies. The pooling of feasibility data with pivotal data to achieve 80 patients with six-month follow-up, does not seem to have been addressed in the protocol. Is this a protocol deviation?

2. While 80 patients (as required by sample size process) have been followed for six months, the remaining 19 enrolled have not. All patients enrolled in the study should have been followed for at least six months. Please complete the study and then resubmit this PMA.

3. The post hoc adequacy of the sample size of 80 patients depends on the clinically sufficient narrowness of the 95% confidence intervals for the **observed** parameter estimates as well as the values of the observed parameters. Please provide clinical justification that these confidence intervals sufficiently establish safety and effectiveness. Were a priori acceptable differences from the estimates established during the sample size estimation process to assure sufficiently narrow confidence intervals around clinically acceptable point estimates?

4. It is not clear that the paired t-tests are performed properly; data should be paired based on patient, not number of episodes. Please either justify your analyses or provide revised analyses based on data paired by patient.

5. Please provide descriptive and inferential analyses by clinical site. Also, provide appropriate analyses by patient demographics.

STATISTICIAN'S CONCLUSIONS

While some of this study's results appear to be promising, the lack of details concerning the a priori study design, the analyses of the results, and the clinical conclusions based the statistical analyses make it impossible to draw meaningful overall statistical conclusions on this device's safety and effectiveness. The sponsor should provide that necessary detail.

If you have any questions concerning this review, please call me at 7-4364.

Gary L. Kamer

cc: Cindy Demian (HFZ-450)
Bram Zuckerman, M.D. (HFZ-450)
Elias Mallis (HFZ-450)
Gerry Gray, Ph.D. (HFZ-542)
DCC (HFZ-401)
BIMO (HFZ-310)
Medical Device File
Board File

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service Food and Drug Administration

MEMORANDUM

DATE: **November 8, 2002**

FROM: Cindy Demian, M.S.
Biomedical Engineer

TO: P020039-Major Deficiency Letter Memo

RE: Cardima, Inc.
Revelation™ Tx Microcatheter Ablation Catheter
NavAblator Ablation Catheter
Naviport™ Guiding Catheter
Revelation™ Tx Select Switch Box
Revelation™ Tx Cables

CONTACT: Marianne Baldwin, Director, Regulatory Affairs (510) 354-0166

Intended use: to deliver RF energy for treatment of atrial flutter and atrial fibrillation (paroxysmal atria fibrillation).

REASON FOR SUBMISSION

The sponsor submitted an original PMA (Module M005), containing the clinical information for their Revelation™ Tx and NavAblator™ Ablation catheters, Naviport™ Guiding catheter, Revelation™ Tx switchbox and cables.

BACKGROUND

The sponsor met with FDA on July 8, 2002, so that both parties could bring the other side up-to-speed since this project changed hands several times since its conception in 1997. The meeting included discussions to include the NavAblator™, and treat the two investigational devices (the Revelation™ Microcatheter & NavAblator™) as a system.

FDA met internally with Dan Shultz, Deputy Director, CDRH, to discuss how to handle this dilemma with two investigational devices, scientifically and regulatory issues. It was decided that the sponsor (if they provided the appropriate data) could submit a PMA.

The sponsor submitted P020039 (the 5th Module) on September 23, 2002. Because the FDA had met with the sponsor previously and advised them on submitting their PMA, Upper Management decided that the sections that they provided in the PMA are fileable, although those sections (clinical and statistical) may not be sufficient. FDA will send major deficiencies.

On October 29, 2002, a meeting was held and it was determined that this PMA should be filed. We discussed the sponsor's request for an expedited review of the PMA. The sponsor will be granted an expedited review because their investigational devices are considered:

Life-threatening or irreversibly debilitating conditions with no alternative modalities. The

condition or potential condition/disease is serious or life-threatening, or presents a risk of serious morbidity and no alternative, legally marketed diagnostic or therapeutic modalities exist.

A key issue which was discussed at this filing meeting was the need for an advisory panel meeting. Because this is new indication for this type of device, FDA will take this to panel. It was noted that a Circulatory System Advisory panel meeting has already been scheduled for late December 2002. The sponsor preferred to attend the December Panel meeting, however, considering that Dr. Ewing needs more data on both devices it is not clear if the sponsor will be ready to participate at the February Panel meeting.

At the filing meeting, Donna-Bea Tilllman, Deputy Director of the Cardiovascular Division, suggested to send the sponsor an email with all of the major and minor deficiencies. However, PMA staff (Nicole Wolanski and Lisa Fisher) recommended that this was not in the Review Team's best interest. Therefore, the sponsor will be sent a major deficiency letter where the letter will state that the sterility issues are still pending.

MODULE SUBMISSIONS

I provided a summary of the review history of the Revelation™ Tx Microcatheter and NavAblator Ablation Catheter System with respect to the individual modules submitted and closed.

M001 -*Biocompatibility*. Deficiencies sent September 28, 2001.

- *A001*-Sponsor responded January 28, 2002 & May 28, 2002.
- *A002*- Sponsor responded May 28, 2002.
- Accepted Module on May 31, 2002. **Closed**.

M002 –*Animal*.

- Accepted Module on September 28, 2002. **Closed**.

M003-*Electrical & Mechanical*

- *Electrical*- Accepted review on August 24, 2001. *Section closed.*
- *Mechanical*-Deficiencies sent March 28, 2002. Sponsor responded April 15, 2002. **Under review.**

M004-*Manufacturing & Sterility*.

- *Manufacturing-Section closed.*
- *Sterility*-**Under Review**.

P020039 (M005) -- Phase I, II, and III clinical. **Under review**.

In addition, two amendments to the PMA Shell were submitted: A001- update of shell plan and A002- change of contact to Ms. Marianne Baldwin.

DEVICE DESCRIPTION

The Revelation Tx system consists of the following components:

- Revelation™ Tx Ablation Microcatheter (3.7F)
- NavAblator™ Ablation Catheter (8F)

14

- Naviport™ Guiding Catheter
- Revelation™ Tx Select Switch Box
- Revelation™ Tx Cables

The Revelation™ Tx Ablation Microcatheter (3.7 F) is a single use, steerable, non-deflectable with an atraumatic, flexible, non-electrically active tip. It has eight electrodes and eight thermocouples temperatures sensors on the distal end of the catheter. This catheter is designed for the treatment of atrial fibrillation by creating linear lesions.

The NavAblator™ Ablation Catheter (8F) is a single use, deflectable with an electrically active tip. It has four electrodes, including one embedded in its tip just proximal to a thermocouple. This catheter is designed for the treatment of atrial flutter in the isthmus region by delivering RF energy to cardiac tissue and is intended for the creation of spot lesions from its tip.

The Naviport™ Guiding Catheter is used to aid in the positioning of the Revelation™ Tx. This exact device has already been cleared through 510(k) for the same intended use.

CONSULTATIONS

• Lesley Ewing, M.D.- Clinical protocol and Labeling	Open Issues
• Gray L. Kamer, Math Statistician- Statistical Analysis	Open Issues
• James Cheng- Electrical Engineering	*Closed Module*
• Cindy Demian, MS- Mechanical Engineering & Biomaterials	Open Issue
• Nick Jensen, D.V.M.- Animal Study	*Closed Module*
• Barbara Crowl, BIMO in OC	Open Issues
• Lisa Kennell- Sterilization	Still Pending
• Susan Jensen- Manufacturing in OC	No Issues thus far

SUMMARY

There were clinical, statistical, BIMO, and minor engineering concerns, see below:

CLINICAL CONCERNS

Dr. Lesley Ewing provided the clinical consult (memo attached). Dr. Ewing provided a detailed summary of the clinical protocol along with her comments. The sponsor was asked to respond to the following major deficiencies:

1. *You have submitted a premarket application for an ablation system that includes two ablation catheters. In your supporting clinical trial one catheter, the Revelation Tx was tested in 95 patients and you have provided 6 month follow-up on 79 of those patients. The other catheter, the NavAblator was tested in 41 patients. In five of these patients, a non-investigational ablation catheter from another manufacturer was required to complete the procedure. The FDA is concerned that the amount of clinical testing you have provided for the NavAblator does not provide a reasonable assurance of safety and effectiveness for this device. Please provide more clinical data for this device or alternatively provide justification for the adequacy of this amount of clinical testing.*

15

2. *You have provided summaries of the follow-up and outcome for the patients involved in the clinical trial. The FDA review team requires more information to thoroughly review your application. Please provide a table of all patients who have been treated with your ablation system. The columns should include the patient identifier, date of procedure, catheters used and numbers(amount) of each, follow-up completed and dates, baseline number of atrial fibrillation episodes, number of atrial fibrillation episodes at 6 months, medications at baseline and at the 6 month assessment.*

3. *You have provided a summary of patient atrial fibrillation episode reduction in terms of amount of patients who had certain frequencies of events at six months. Please provide a complete tracking of the change in event frequency per patient or patient group. For example your study included 14 patients who had 3 events per month at baseline, what was the status of these 14 patients at the 6 month follow-up. This data would necessitate the removal of the 5 patients who did not have an accurate baseline frequency recorded. Please provide the identifiers of those 5 patients.*

4. *You have provided summary adverse event information for your clinical trial. In order to perform a complete review the FDA review team requires additional information on patients [redacted] Please provide a summary of the adverse events that occurred and provide all the data monitoring forms and any other information, such as discharge summaries, used for your assessment of these adverse events.*

5. *You have provided summary data for all the patients treated with your ablation system and this includes patients who have been treated with non-investigational ablation devices, including a cooled ablation catheter. Please provide justification, both clinical and statistical, for pooling this data. This justification should include the effectiveness data assessment for the patients who were treated only with the investigational device and comparison with the group treated with both the investigational device system and other devices. Please explain why the patients who required treatment with a non-investigational device should not be treated as failures of your device system.*

6. *Your clinical trial includes many variables, such as many different devices, different ablation procedures performed, and different study protocols for different phases of the investigation. Please provide a statistical justification for pooling the data generated by the trial.*

7. *The secondary effectiveness endpoint of your clinical trial was improvement in quality of life as measured by two instruments, the SF-36 and the Atrial Fibrillation Severity Scale, compared to baseline measurements. You have provided the mean scores and standard error for baseline, three month and six month follow-up. Please provide the number of patients who achieved a clinically significant improvement or worsening from baseline to the six month follow-up for the total group and for the subgroups of patients by baseline episode rate. Please provide the details of how the QOL questionnaires were*

16

administered. Also, please address adjustment for placebo effect in this single arm unblinded clinical trial.

8. *The acute procedural endpoint was dropped from the clinical trial protocol between phases IIb and III. Please explain how the investigators in phase III determined when they had produced effective lesions. Is it your intention that the ablation procedure would be strictly anatomically based? Are you intending to recommend measurement of bi-directional block to assess the adequacy of the tricuspid isthmus ablation line?*

9. *The primary effectiveness endpoint of the trial was decrease in frequency of atrial fibrillation episodes from baseline to 6 months follow-up. This was assessed by transtelephonic event recordings which were described as "mandatory" weekly in month three and six. This is not described in the investigational protocol. Please provide an assessment of compliance with the transtelephonic recordings per patient. Was there any other method in place to determine if patients were having symptoms not reported?*

10. *Please provide details of the baseline monitoring period per patient. This should include number of recorded events and their electrocardiographic diagnosis, such as sinus tachycardia, atrial fibrillation, etc. Please add the calculation of the percentage of recordings per patient that were diagnosed to be atrial fibrillation.*

11. *In the initial review of your clinical summary it appears that you have included the 11 patients who withdrew from the study after having an ablation procedure in your assessment of effectiveness. Please provide a justification for this approach, especially for the 6 patients who subsequently were treated with a pacemaker and the 2 who had a MAZE procedure after the ablation procedure. Please provide the identifier numbers for these patients and the details of their treatment in your effectiveness assessment.*

12. *You have provided a list of all the adverse events reported by the investigators arranged alphabetically by adverse event. Please provide a list of adverse events grouped by patient.*

13. *Table F-18, page 64 of your submission, shows the baseline number of symptomatic atrial fibrillation episodes that occurred in the patient population of your study. It appears that there may be two groups of patients, grouped around 3-4 episodes per month and again at 10-19 episodes per month. The FDA is concerned that this bimodal distribution may represent a difference the patient's disease process. Please justify the pooling of all these patients.*

STATISTICAL CONCERNS

Gary Kamer provided the statistical consult (memo attached). Mr. Kamer provided a detailed summary of the study protocol along with his comments. The sponsor was asked to respond to the following major deficiencies:

17

1. *Please provide statistical and clinical justification for the pooling of the data from the Expanded Feasibility and Pivotal studies. The pooling of feasibility data with pivotal data to achieve 80 patients with six-month follow-up, does not seem to have been addressed in the protocol. Is this a protocol deviation?*

2. *While 80 patients (as required by sample size process) have been followed for six months, the remaining 19 enrolled have not. All patients enrolled in the study should have been followed for at least six months. Please complete the study and then resubmit this PMA.*

3. *The adequacy of the sample size of 80 patients depends on the clinically sufficient narrowness of the 95% confidence intervals for the observed parameter estimates. Please provide clinical justification. Were a priori acceptable differences from the estimates established during the sample size estimation process to assure sufficiently narrow confidence intervals?*

4. *It is not clear that the paired t-tests are performed properly; data should be paired based on patient, not number of episodes. Please either justify your analyses or provide revised analyses based on data paired by patient.*

5. *Please provide descriptive and inferential analyses by clinical site. Also, provide appropriate analyses by patient demographics.*

ENGINEERING CONCERNS

Mr. James Cheng, Electrical Engineer and Software Expert, provided the electrical engineering consult for the Module 3. Mr. Cheng provided a detailed summary testing along with his comments. Mr. Cheng did not cite any major deficiencies, therefore, his portion of M003 is considered closed, unless there is a reason to re-open the module.

I provided the mechanical engineering portion for the Module 3. It was clear after several discussions internally and with the sponsor that the NavAblator was to be used in conjunction with the Revelation Tx Microablation catheter (and were to be used a system). Because it was not clear with regards to the issues revolving the NavAblator, I did revisit and made sure that both ablation catheters were tested (in the animal study, electrical engineering, mechanical engineering, and materials were biocompatible [sterility is still pending Lisa Kennell's review]). During Dr. Ewing's initial review of the PMA, she did bring to my attention the Customer Experience Reports, in which there were corrective actions that were not resolved. I did cite these issues as minor deficiencies, in which the sponsor will be asked to respond to the following:

1. Referring to the Customer Experience Reports, Table F-43, page 111 in Volume 1 of the PMA, please address the following:

    a. You report ID 2002000261 which occurs on both pages 117 and 118 at two different cites (General Hospital Center at Passaic and Inova Fairfax Hospital). This would seem to indicate that the ID numbers are not unique to a specific event or procedure. Please describe how these Customer Experience Reports IDs are identified and tracked.

18

b. For the reports that generated corrective actions, please confirm that these corrective actions were implemented. Please also confirm that the manufacturing module (M004) which was submitted reflects the updated processes containing the corrective actions. In addition, please provide a cross reference that calls out where the corrective actions are implemented in the manufacturing module.

BIMO CONCERNS

Ms. Crowl, (BIMO) noted that the sponsor should provide more information with regards to line data, patient consent forms, and addresses of the investigational sites, refer to email sent October 31, 2002. The sponsor responded by email on November 5, 2002 to FDA's request. Ms. Crowl is still requesting line data, which is covered in the Dr. Ewing's deficiency 4, refer to the concerns above.

STERILIZATION CONCERNS – STILL PENDING

Lisa Kennell will provide the sterilization consult and the sponsor will be notified of the following:

Please be advised that sterility issues regarding your PMA submission are still pending at this time.

RECOMMENDATION – Major Deficiency Letter

Cindy Demian, M.S.

Cindy Demian, MS., Lead Reviewer
Cardiac Electrophysiology & Monitoring Branch

8 Nov 2002
Date

Concur

Elias Mallis

Elias Mallis, Branch Chief
Cardiac Electrophysiology & Monitoring Branch

11/13/02
Date

19

Ms. Marianne E. Baldwin
Vice President, Regulatory, Clinical, Quality
Cardima, Inc.
47266 Benicia Street
P.O. Box 14172
Fremont, CA 94538

NOV 14 2002

Re: P020039
REVELATION® Tx Microcatheter with NavAblator Ablation System
Filed: September 23, 2002
Amended: November 6, 2002

Dear Ms. Baldwin:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial scientific review of the above referenced premarket approval application (PMA). We regret to inform you that on the basis of this review, we have concluded that the PMA lacks information needed to complete the review and determine whether there is reasonable assurance that the device is safe and effective for its intended use.

Because of this lack of information, review of the PMA cannot continue and, accordingly, we have listed the following significant deficiencies which require the responses as indicated:

1. The PMA submission requests approval for two different ablation catheters, the Revelation Tx and NavAblator. In your supporting clinical trial, the Revelation Tx was tested in 95 patients and you provided 6 month follow-up on 79 of those patients. The NavAblator was tested in 41 patients, five of which required a non-investigational ablation catheter from another manufacturer to complete the procedure. FDA is concerned that the amount of clinical evidence provided for the NavAblator may not provide a reasonable assurance of safety and effectiveness for this device. Please provide additional clinical evidence on the NavAblator or, alternatively, justify why the amount of testing already provided provides a reasonable assurance of safety and effectiveness.

2. You provided summaries of the follow-up and outcome for the patients involved in the clinical trial. Additional information is needed in order for FDA to thoroughly review your application. Please provide a table of all patients who have been treated with your ablation system. The columns should include the patient identifier, date of procedure, identify and number of catheters used, follow-up completed and dates, number of atrial fibrillation episodes at baseline, number of atrial fibrillation episodes at 6 months, medications at baseline, and medications at the 6 month assessment.

3. You provided a summary of patient atrial fibrillation episode reduction in terms of number of patients who had certain frequencies of events at six months. Please provide a complete tracking of the change in event frequency per patient or patient group. For example, for the group of 14 patients who had 3 events per month at baseline, please identify the status of these 14 patients at the 6 month follow-up. This data presentation necessitates the removal of the 5 patients who did not have an accurate baseline frequency recorded. In addition, please provide the patient identifiers of those 5 patients.

4. You provided summary adverse event information for your clinical trial. Please provide additional adverse event information on patients [redacted] Specifically, provide a summary of the adverse events that occurred and provide all the data monitoring forms and any other information, such as discharge summaries, used for your assessment of these adverse events.

5. You provided summary data for all patients treated with your ablation system, including patients who were treated with non-investigational ablation devices, such as a cooled ablation catheter. Please provide clinical and statistical justification for pooling these data. Your justification should include the effectiveness data assessment for the patients treated only with the investigational device and comparison with the group treated with both the investigational device system and other devices. Please explain why the patients who required treatment with a non-investigational device should not be treated as device failures.

6. Your clinical trial includes many variables, such as different devices, different ablation procedures performed, and different study protocols for different phases of the investigation. Please provide a statistical justification for pooling the data generated by the trial, given these variables in the study.

7. The secondary effectiveness endpoint of your clinical trial was improvement in quality of life (QOL) as measured by two instruments, the SF-36 and the Atrial Fibrillation Severity Scale, and measured at baseline and at various post-treatment time points. You provided the mean scores and standard error for the instrument scores at baseline, three month and six month follow-up. Please provide the number of patients who achieved a clinically significant improvement or worsening from baseline to the six month follow-up for the total group and for the subgroups of patients stratified by baseline episode rate. Please explain in detail how the QOL questionnaires were administered. Also, please address adjustment for placebo effect, given that the clinical study was consisted of a single arm and was unblinded.

8. The acute procedural endpoint was dropped from the clinical trial protocol between phases IIb and III. Please explain how the investigators in phase III determined when they had produced effective lesions. Please clarify whether you intended the ablation procedure to be strictly anatomically based. Please explain whether you intend to recommend measurement of bi-directional block to assess the adequacy of the tricuspid isthmus ablation line.

9. The primary effectiveness endpoint of the trial was decrease in frequency of atrial fibrillation episodes from baseline to 6 months follow-up. This was assessed by transtelephonic event recordings which were described as "mandatory" weekly in months three and six. This is not described in the investigational protocol. Please provide an assessment of compliance with the transtelephonic recordings per patient. Explain whether any other method was established and used to determine if patients were having symptoms not reported.

10. Please provide details of the baseline monitoring period per patient. This should include number of recorded events and their electrocardiographic diagnosis, such as sinus tachycardia, atrial fibrillation, etc. Please add the calculation of the percentage of recordings per patient that were diagnosed to be atrial fibrillation.

11. Based on our review of your clinical summary, it appears that you included the 11 patients who withdrew from the study after having an ablation procedure in your assessment of effectiveness. Please justify using this approach, especially for the 6 patients who were subsequently treated with a pacemaker and the 2 patients who had a MAZE procedure after the ablation procedure. Please provide the identifier numbers for these patients and the details of their treatment in your effectiveness assessment.

12. You provided a list of all the adverse events reported by the investigators, arranged alphabetically by adverse event. Please provide a list of adverse events grouped by patient.

13. Table F-18, page 64 of your submission, shows the baseline number of symptomatic atrial fibrillation episodes that occurred in the patient population of your study. It appears that there may be two groups of patients, grouped around 3-4 episodes per month and again at 10-19 episodes per month. FDA is concerned that this bimodal distribution may represent a difference in the patient's disease process. Please justify the pooling of all these patients.

14. While 80 patients (as required by sample size process) have been followed for six months, the remaining 19 enrolled have not. All patients enrolled in the study should have been followed for at least six months. Please submit an updated clinical report that includes study results from these addition 19 patients.

15. The adequacy of the sample size of 80 patients depends on the clinically sufficient narrowness of the 95% confidence intervals for the observed parameter estimates. Please provide clinical justification. Were a priori acceptable differences from the estimates established during the sample size estimation process to assure sufficiently narrow confidence intervals?

16. It is unclear that the paired t-tests were performed properly; data should be paired based on patient, not number of episodes. Please either justify your analyses or provide revised analyses based on data paired by patient.

17. Please provide descriptive and inferential analyses by clinical site. Also, provide appropriate analyses by patient demographics.

18. Please address the following issues related to the Customer Experience Reports, supplied in Table F-43, page 111 in Volume 1 of the PMA:

    a. You report ID 2002000261, which occurs on both pages 117 and 118 at two different cites (General Hospital Center at Passaic and Inova Fairfax Hospital). This suggests that the ID numbers are not unique to a specific event or procedure. Please describe how these Customer Experience Reports IDs are identified and tracked.

    b. For the reports that generated corrective actions, please confirm that these corrective actions were implemented. Please also confirm whether the manufacturing module (M004) reflects the updated processes containing the corrective actions. Finally, please provide a cross reference that calls out where the corrective actions are implemented in the manufacturing module.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your PMA application can be completed, and reflect the completion of our review except for the sterilization section of the PMA application. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

This letter reflects the current progress of our review of your application. Please be advised that further substantive review of your application or any response to this letter may result in additional deficiencies.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA number and will be subject to the requirements of 21 CFR 814.20.

You may amend the PMA to provide the above requested information (6 copies), voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information (3 copies) or request an extension. The required copies of the amended PMA should include the FDA reference number for this PMA and should be submitted to the following address:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Upon receipt of an amendment adequately addressing the above requests or a written response declining to submit the requested amendment, CDRH may schedule an advisory panel meeting at which your PMA will be reviewed. You will be notified of the location and date of this meeting should one be necessary. Any additional information to be included in your PMA should be submitted in the form of a PMA amendment and be received by FDA at least 6weeks in advance of the scheduled advisory panel meeting in order for FDA and the panel members to have adequate time to review the new information. Information received by CDRH less than 6 weeks in advance of a scheduled advisory panel meeting will not be considered or reviewed at the meeting and may delay consideration of your PMA until a subsequent advisory panel meeting.

If you have any questions concerning this deficiency letter, please contact Cindy Demian, M.S. at (301) 443-8517.

Sincerely yours,

/S/

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

7.0 Results

This PMA Application is reporting the results of the 109 subjects treated as of July 31, 2002. Of the 109 treated subjects, ten (10) were part of the feasibility study and the safety outcomes from the 6-month follow up duration for these Feasibility subjects are reported separately in Appendix V-2. Of the remaining 99, 80 have completed a minimum of 6 months of follow up, 53 have completed 12 months of follow up, and 29 have completed 24 months. The characteristics of the study subjects and the outcomes to date for these subjects at specified follow up intervals are presented in the following pages.

Assessment measurements to be reported include patient health changes from baseline to six months for effectiveness and the incidence of adverse events/complications throughout entire study participation and procedural characteristics, including catheter performance.

7.1 Study Participation

Twenty-three (23) investigational sites have enrolled in this study and three (3) of them have withdrawn (at Cardima's request) because they were not successful in enrolling study subjects. The study sites are identified in Table F-6. The Institutional Review Board (IRB) organizations for those sites who continue in this study are identified in Table F-7.

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

Table F-6, List of Investigators and Subjects Treated

Principal Investigator	Clinical Investigational Site	Study Phase	Subjects per Site
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

Table F-6, List of Investigators and Subjects Treated

Principal Investigator	Clinical Investigational Site	Study Phase	Subjects per Site
Kara Quan, MD	MetroHealth Cleveland, OH	III Withdrawn	0
Eli S. Gang, MD	Access Clinical Trials Beverly Hills, CA	III	1
Bruce B. Lerman, MD	Cornell University New York, NY	III	0
Arjun D. Sharma, MD	Regional Cardiology Associates Sacramento, CA	III	0
Total			109

Table F-7- IRB Information

Investigational Site	IRB Contact
Stanford Medical Center Palo Alto, CA	David Gaba, MD, Chair Panel on Medical Human Subjects Stanford University 1215 Welch Road, Modular A Palo Alto, CA 94305
Massachusetts General Hospital Boston, MA	Elizabeth Hohmann, MD, Chair Human Research Committee Massachusetts General Hospital Lawrence House-10 North Grove St. Boston, MA 02114-2698
The Johns Hopkins Hospital Baltimore, MD	Lewis C. Becker, MD, Chair The Johns Hopkins University School of Medicine The Johns Hopkins Hospital Joint Committee on Clinical Investigations Turner 36 School of Medicine 720 Rutland Avenue Baltimore, MD 21205-2196
Mayo Clinic Rochester, MN	Eugene Dimagno, MD, Chair Institutional Review Board Mayo Research Services 200 First Street, SW Rochester, MN 55902

Table F-7- IRB Information

Investigational Site	IRB Contact
Inova Institute for Research and Education Falls Church, VA	Margaret Hanson, MPA, CIP Inova IRB Administrator Inova Institutional Review Board 3300 Gallows Road Falls Church, VA 22042
Main Line Health Heart Center Wynnewood, PA	Albert A. Keshgegian, MD, PhD, Chair Main Line Hospitals Institutional Review Board 100 Lancaster Avenue Wynnewood, PA 19096
University of Chicago Chicago, IL	Jonathon Moss, MD, PhD, Chair University of Chicago Institutional Review Board 5841 South Maryland Avenue AMB-S144 MC 1108 Chicago, IL 60637
New England Heart Institute Manchester, NH	Eleanor Dahar, ESQ, Chair Catholic Medical Center/Institutional Review Board 100 McGregor Street Manchester, NH 03012
Lancaster Heart Foundation Lancaster, PA	James A Wilson, MD, Chair Lancaster General Hospital Institutional Review Committee 555 North Duke Street PO Box 3555 Lancaster, PA 17604-3555
Diagnostic Center of CV Diseases Chattanooga, TN	William C Jacobs, BA, Chair Western Institutional Review Board 3535 7th Avenue SW Olympia, WA 98502
EHI-Atlantic Health System Cardiac Medicine & Electrophysiology Warren, NJ	John G Cubero, MD, Chair The General Hospital Center at Passaic Institutional Review Committee 350 Boulevard Passaic, NJ 07055
Carle Heart Center Urbana, IL	David W. Main, MD, MPH, Chair Carle Institutional Review Board Carle Foundation Hospital 611 West Park Street Urbana, IL 61801-2595
NYU Medical Center New York, NY	Keith M. Krasinski, MD, Chair Bellevue Hospital Center 462 First Avenue, 8W51 New York, NY 10016

Table F-7- IRB Information

Investigational Site	IRB Contact
Wisconsin Center for Clinical Research, St. Francis Hospital Milwaukee, WI	Sharon Lynn Nelson, MSN, RN, CNS, Chair Schulman Associates IRB, Inc. 4290 Glendale, Milford Rd Cincinnati, OH 45237
Wisconsin Center for Clinical Research, St. Luke's Hospital Elkhorn, WI	Martin Oaks, MD, Chair Aurora Health Care IRB Winter Research Building 836 North 12th Street PO Box 342 W310 Milwaukee, WI 53201-0342
Cardiac Arrhythmia Consultants Ltd. Chicago, IL	Joal Hill, JD, MPh, PhD(c), Chair Advocate Institutional Review Board 1775 Dempster, 8 South Parkridge, IL 60068
Harper University Hospital Detroit, MI	Manuel Tancer, MD, Chair Wayne State University Human Investigation Committee 4201 St Antoine Boulevard - UHC-6G Detroit, MI 48201
Sequoia Hospital Redwood City, CA	Fred Marcus, MD, Chair Sequoia Hospital CHW 170 Alameda de las Pulgas Redwood City, CA 94062-2799
Access Clinical Trials / Cardiovascular Research Institute Beverly Hills, CA	Jack Coburn, MD, Chair Brotman Medical Center, Tenet Health System 3828 Delmas Terrace Culver City, CA 90231
Cornell University New York, NY	David Behrman, DMA, Chair The New York Presbyterian Hospital - Weill Medical College of Cornell University Committee on Human Research 425 East 61st Street, Suite DV301 New York, NY 10021
Regional Cardiology Associates Sacramento, CA	Craig D. Weiner, MD, Chair Regional Institutional Review Board 6501 Coyle Avenue Carmichael, CA 95608

7.2 Device Accountability

The accounting of investigational devices shipped and used as of July 31, 2002 is summarized in Table F-8 and Table F-9.

Table F-8, Number of REVELATION® Tx Catheters

Site #	Quantity Shipped	Quantity Used	Quantity Returned	Quantity at Site
Phase I				
01	6	5	1	0
02	8	5	3	0
03	11	9	2	0
Total	**25**	**19**	**6**	**0**
Phase II				
02	9	7	2	0
03	13	7	6	0
04	4	3	1	0
05	18	13	5	0
06	16	14	2	0
07	6	4	2	0
08	19	8	11	0
09	13	7	6	0
10	11	11	0	0
Total	**109**	**74**	**35**	**0**
Phase III				
01	0	0	0	0
02	0	0	0	0
03	4	2	0	2
05	15	7	7	1
06	10	4	5	1
08	2	1	1	0
09	2	0	2	0
10	15	7	3	5
11	8	5	1	2
14	19	16	1	2
15	2	1	1	0
16	18	11	3	4

Table F-8, Number of REVELATION® Tx Catheters

Site #	Quantity Shipped	Quantity Used	Quantity Returned	Quantity at Site
17	6	3	2	1
18	7	4	1	2
19	5	3	1	1
21	6	2	0	4
22	0	0	0	0
23	2	0	0	2
Total	**121**	**66**	**28**	**27**

Table F-9, Number of NavAblators Shipped

Site #	Quantity Shipped	Quantity Used	Quantity Returned	Quantity at Site
01	0	0	0	0
02	0	0	0	0
03	3	1	2	0
05	11	6	4	1
06	14	6	4	4
08	2	1	1	0
09	2	0	2	0
10	6	1	5	0
11	7	4	0	3
14	20	14	1	5
15	4	1	3	0
16	17	11	6	0
17	7	1	3	3
18	10	4	2	4
19	8	3	4	1
21	12	1	0	11
22	0	0	0	0
23	4	0	0	4
Total	**127**	**54**	**37**	**36**

7.3 Subject Accountability

All told, 109 subjects were treated with the REVELATION® Tx Cardiac Ablation System. Ten (10) of those subjects were treated in Phase I (IIa) and reported separately. The remaining ninety nine (99) subjects were part of phases IIb and III.

Those ninety nine subjects came from a total of 195 subjects who enrolled and entered the baseline monitoring period. Of those 195 eighty four (84/195, 43%) did not present for treatment because they either withdrew or failed the baseline monitoring period. Additionally, twelve (12/195, 6/15%) had not yet completed the 30-day monitoring period at the time the database was closed to new data.

Figure F-2 illustrates the disposition of all 195 subjects who were screened for the study and the status of study subjects through the course of the study.

Data are presented here for the demographics and medical history characteristics for ninety-five (95) of these ninety-nine (99) subjects because four (4) of the ninety-nine were treated too recently to have collected and verified their data at the time data analysis began.

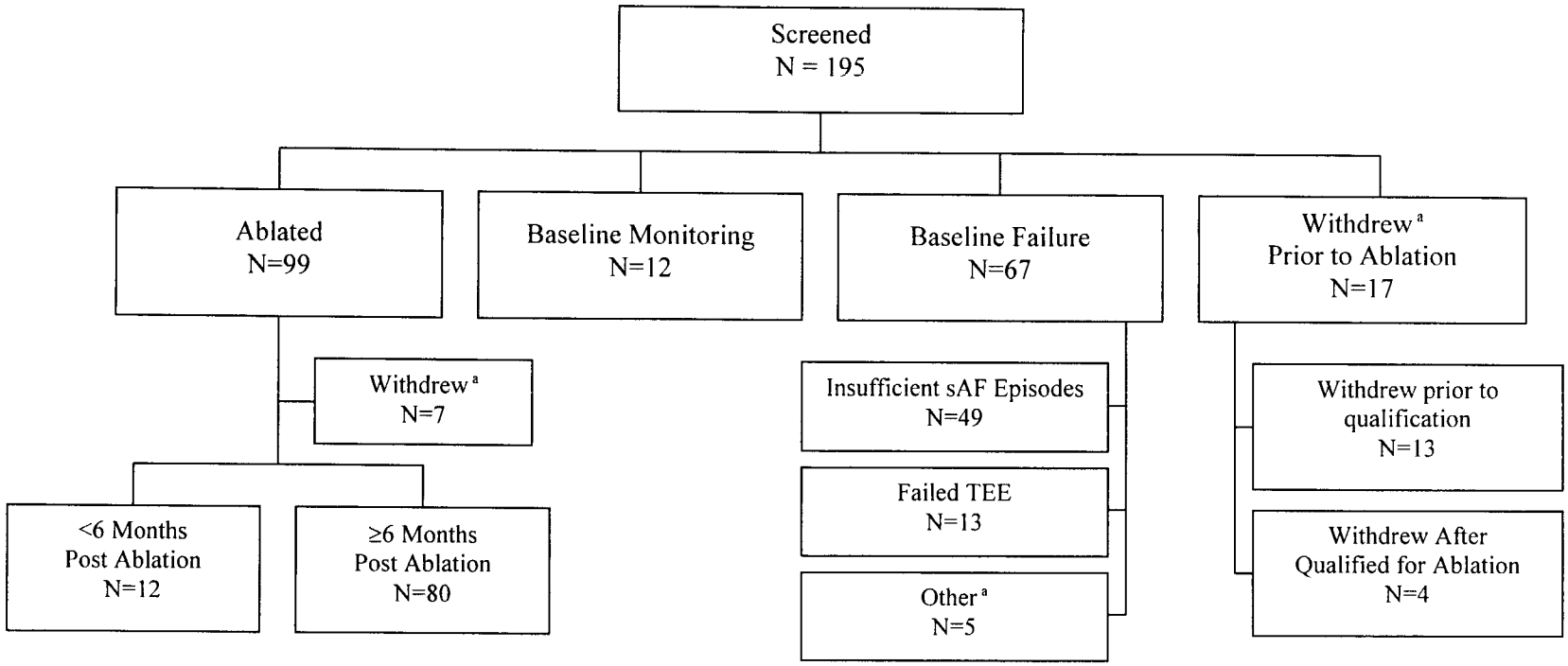
In addition, three (3) of these ninety-five subjects received a second treatment with the REVELATION® Tx Cardiac Ablation System (as permitted by the protocol), therefore, procedural characteristics are presented for a maximum of ninety-eight (98) procedures in ninety-five (95) patients.

Follow up data are presented for those subjects who had achieved the follow up interval whose data had been verified and entered into the database as of July 31, 2002. Those denominators vary from one interval to another but begin with a base of ninety five (95) subjects.

Figure F-3 is a graphic illustration of the subject evaluation population by assessment intervals, including attrition. The number of subjects who have achieved the scheduled follow up assessment interval are included in Figure F-3. These numbers represent the maximum possible sample size for any visit and

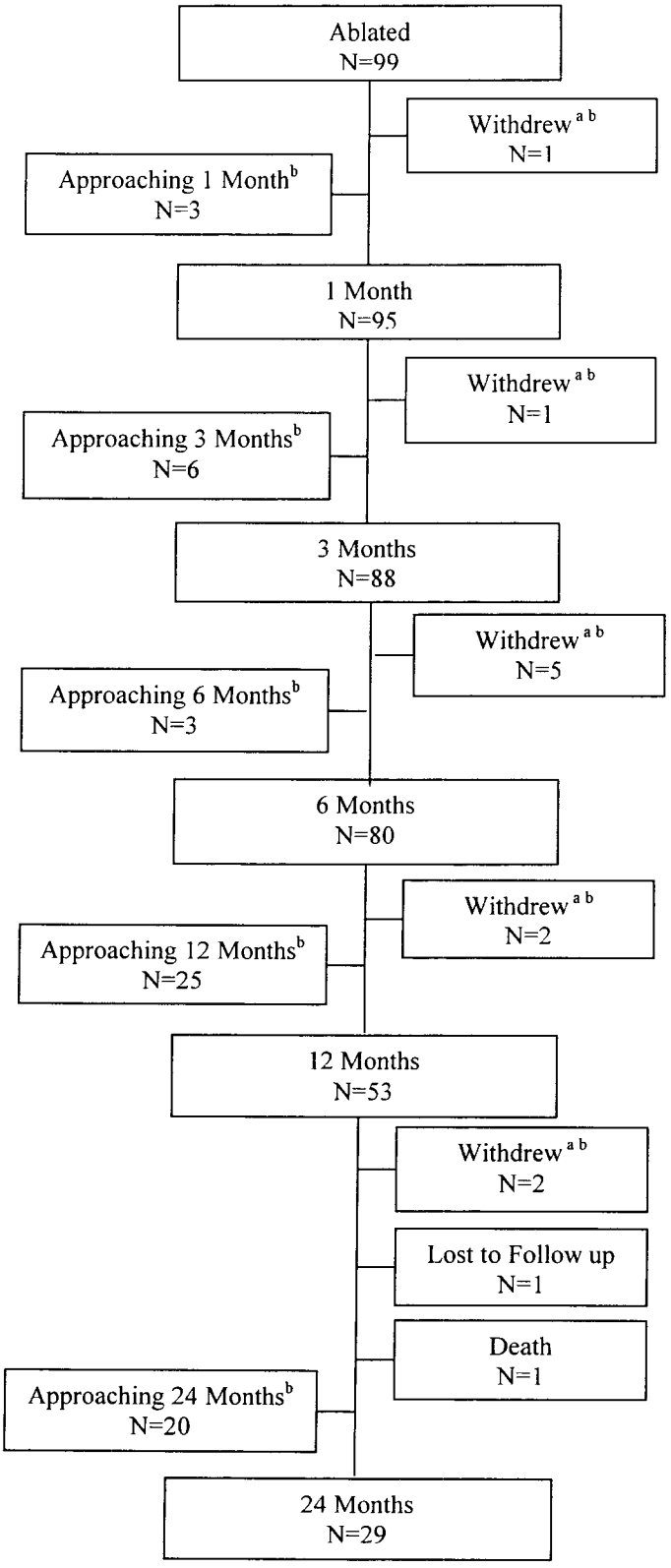
variable. Existing follow up data for this population are quite complete, however, because this study is ongoing, many subjects are between evaluation visits and data for some completed evaluations had not been processed at the time the data analysis began.

Figure F-2, Subject Accountability



[a] Reasons for withdrawal are presented by patient in Tables F-10

Figure F-3, Subject Accountability by Assessment Interval



[a] Reasons for withdrawal are presented by patient in Table F-11
[b] Not cumulative from interval to interval

78

The number of eligible subjects whose data are included in the evaluation of follow up outcomes varies due to attrition and "matriculation" of the subjects from one follow up interval to the next, as illustrated in Figure F-3.

In addition, not all data for those subjects who had achieved a given interval were verified and available for analysis at the time data analysis began. These varying denominators at each interval are reported in the tables summarizing the outcomes.

As noted above, some subjects withdrew from the study. The reasons for subject withdrawal are varied both in timing and fact. Some subjects withdrew before they completed their baseline monitoring period as summarized in Table F-10

Table F-10, Pre-Ablation Withdrawals (n=17)

Category	Frequency
Decision Change - No Longer Wanted to Pursue Study	10
Concurrent Cancer Therapy	2
No Reason Stated	1
Denied of Insurance Payment[a]	1
Generator Failure on Ablation Day[a]	1
Other Arrhythmias Requiring Different Treatment[a]	1
Preferred PV and LA Ablation[a]	1

[a] Withdrew after qualifying for ablation

[b] Generator failure forced the use of a non-study system

Table F-11 below, summarizes the reported reasons for withdrawal for those subjects who withdrew after ablation during the follow up phase of the study.

Table F-11, Post-Ablation Withdrawals (n=11)

Study Interval	Frequency	Pt. ID
PPM insertion	6	(IIb)
No reason stated	2	(IIb
Moved out of state	1	(III)
Maze procedure	2	(IIb)

In addition, there were sixteen patients who elected to re-screen because they failed to meet the inclusion criterion for symptomatic episodes. Of those sixteen, four (4) qualified for treatment after the second screening period by having at least nine (9) symptomatic episodes in a total of 90 days. Of the remaining re-screened patients, one withdrew (and is included in the seventeen listed as having withdrawn before qualifying for ablation in Figure F-2) and the other nine (9) did not have the required number of episodes. Re-screened patients are tabulated in Table F-12.

Table F-12, Re-Screened Subject Accountability (n=16)

Category	Frequency	%
Qualified for Ablation	4	25.00
Failed 90-Day Screening Period	9	56.25
90-Day Re-Screening In Progress	2	12.50
Withdrew*	1	6.25
Total	16	100.00

*No longer wanted to continue with the weekly transmissions

7.4 Baseline Patient Characteristics and Assessments

Among the 95 subjects included in this report, males outnumbered females by approximately 3:1, or 75.8% males (Table F-13). The mean age overall was 57.8 years (±10.6) with males somewhat younger, mean age 56.4 years (±10.2), than females, mean age 62.0 (±10.7) years.

Table F-13 - Subject Age and Gender (n=95)

Gender	Age in years Mean ± SD	Age Range in Years	Frequency	%
Female	62.0 ± 10.7	27.9–77.1	23	24.2
Male	56.4 ± 10.2	35.3–75.9	72	75.8
Total	57.8 ± 10.6	27.9–77.1	95	100.0

7.4.1 Medical History

The medical history of each subject was collected to characterize the clinical profile of the study subjects. The profile is summarized by major category in Table F-14.

Most subjects, (71/95, 74.7%), presented with a history of concomitant cardiovascular conditions other than atrial fibrillation. Histories of musculoskeletal and gastrointestinal conditions were also relatively common with approximately one third of the subjects noted to have these conditions. Nearly one-quarter of the subjects (22/95, 23.2%) also had a history of respiratory or endocrine.

Table F-14 Medical History

Condition	Frequency[a] (n=95)	%
Cardiovascular	71	74.7
Musculoskeletal	33	34.7.
Gastrointestinal	32	33.7
Respiratory	22	23.2
Endocrine	22	23.2
Neurological	20	21.1
Other	19	19.1
Renal	14	14.7
None Reported	9	9.1
Psychological	7	7.4
Immunologic	5	5.3
Hematopoietic	2	2.1
Lymphatic	1	1.1

[a] Many subjects reported more than one concomitant medical condition

More than two thirds of the study subjects (67/95, 70.5%) reported no prior cardiac interventions (Table F-15). Of the 95 subjects, only 8 reported prior DC cardioversions, consistent with the nature of paroxysmal AF which is, by definition, self-terminating.

Table F-15, Patients with Previous Cardiac Interventions (n=95)

Type of Intervention	Frequency[a]	%
No Prior Cardiac Interventions	67	70.5
RF Ablation	24	25.3
DC Cardioversion	8	8.4
Pacemaker	7	7.4
CABG	7	7.4
PTCA/Stent	5	5.3
Angioplasty	2	2.1

[a] Some patients had more than one prior cardiac intervention

7.4.2 NYHA Status

More than three fourths of the subjects (72/93, 77.4%) had no limitations of activities and were thus NYHA Class I (Table F-16), with the remaining approximately one-quarter of the subjects (21/93, 22.6%) having slight limitations (NYHA Class II).

Table F-16 Pre-procedure NYHA Class

NYHA Class	Definition	Freq.	%
I	No limitations of activities: no symptoms from ordinary activity.	72	77.4
II	Slight limitation of activity: comfortable at rest or with slight exertion.	21	22.6
III	Marked limitation of activity: comfortable only at rest.	0	0.0
IV	Confined to a bed or chair; any physical activity brings on discomfort and symptoms also occur at rest.	0	0.0
Total		93*	100.0

* Two subjects with unstated NYHA category

7.4.3 Arrhythmia Symptoms

The baseline incidence ("Presence") and severity ("Severity") of the five most common symptoms associated with cardiac arrhythmias are presented in Table F-17. The severity of each symptom was self-reported on a five-point scale with five (5) being the most severe and three (3) being "moderate" severity. Table F-17 summarizes the incidence of those reports of symptoms and proportion of those with a severity rating of '3' or greater (at least "moderate").

Table F-17, Presence and Severity of Common Arrhythmia Symptoms (n=95)

Symptom	Presence Freq. (%)	Severity (≥3) Freq./n (%)
Palpitations	85 (89.5)	62/76 (81.6)
Fatigue	53 (55.8)	37/46 (80.4)
Shortness of Breath	46 (48.4)	31/44 (70.4)
Lightheadedness	33 (34.7)	24/31 (77.4)
Other	28 (29.5)	19/24 (79.2)
Chest Pain	19 (20.0)	11/19 (57.9)
No Symptoms Reported	1 (1.1)	NA

[a] Some subjects reported more than one symptom and not all reports of symptoms were accompanied by reports of severity.

Palpitations were reported by nearly all subjects (85/95, 89.5%) and fatigue was also relatively commonly reported (53/95, 55.8%). Approximately one half (46/95, 48.4%) of the subjects reported shortness of breath while relatively fewer subjects reported lightheadedness or chest pain, 34.7% and 20.0%, respectively. At least 70% of the subjects rated the severity of the reported symptom to be of at least 'moderate' severity, except for chest pain, where only 57.9% (11/19) of the reporting subjects rated the severity as 'moderate'.

Note that while all study subjects reported whether or not they had symptoms and the nature of the symptom, they did not always report severity, so the denominator for the severity does not always match the denominator for the frequency ("presence").

7.4.4 Baseline Atrial Fibrillation Episodes

All subjects are instructed to closely monitor their symptomatic episodes during the 30-day baseline monitoring period. The subjects are blinded to how many episodes they need to qualify for the study and are not told that they qualify for the study at all until after they transmit a minimum of three (3) symptomatic episodes, the 30-day period is nearly completed, and the transmission records have been confirmed by an independent cardiologist working with the event monitoring service. Table F-18

summarizes the results of the episode recordings reported via event monitor card transmissions by the 95 subjects included in this evaluation.

The mean number of symptomatic baseline episodes transmitted during thirty-day baseline monitoring by these study subjects was 9.9 (±9.1) and the median episode frequency was 7 episodes. Nearly one third (31/95, 32.2%) of the subjects had 10 or more symptomatic episodes during the 30-day baseline monitoring.

Table F-18 -Baseline Number of Symptomatic Atrial Fibrillation Episodes (n=95)

Number of Episodes	Baseline Frequency	
	Freq	%
3	14	14.7
4	15	15.8
5	7	7.4
6	9	9.5
7	4	4.2
8	6	6.3
9	9	9.5
10-14	16	16.8
15-19	5	5.1
20-29	6	6.1
30+	4	4.2
Total	**95**	**100.0**
Mean, SD	**9.9 ± 9.1**	
Median	**7.0**	

A graphic representation of the episode frequency distribution for these study subjects during their baseline monitoring period is presented in Figure F-4.

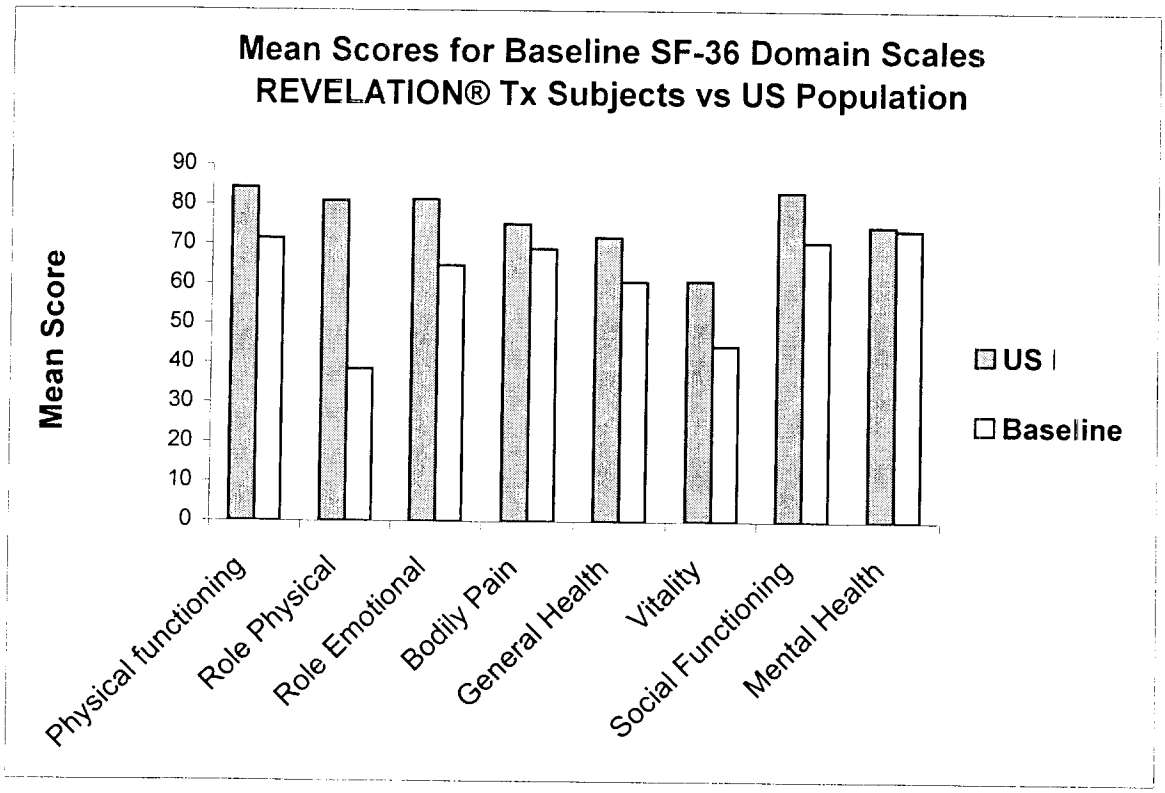


Figure F-4, Baseline SF-36 Mean Scores Compared to US Population Norms

7.4.5 Quality Of Life

Atrial fibrillation is known to have a detrimental effect on one's quality of life, even when non-symptomatic, due to the accompanying cardiac dysfunction. However, symptomatic patients have a greater awareness of their arrhythmia and, therefore, a greater sensitivity to its effects on their lives. A highly symptomatic patient could experience a significant improvement in quality of life if the frequency and/or severity of the symptomatic episodes were reduced.

There are two recognized instruments often used to measure the quality of life in patients with cardiac conditions and both of them are used in this study.

SF-36

The Medical Outcomes Study Short Form 36 (commonly referred to simply as the SF-36) is a validated instrument that is used for the purpose of assessing general quality of life. The responses to questions on this instrument can be used to establish scores for eight scales representing various domains of quality of life. Each scale takes on values from 0 to 100 with higher values signifying better health status. The domain scores determined for the subjects of this study were established by employing the methods from the SF-36 manual. The "normal" values for each domain are based upon the mean values derived from scoring of the "general population", presumed to be representative of a generally healthy population. These "normal" values were collected using the same questionnaire in 1994 by the developer of the SF-36, John E Ware, Jr., Ph.D. The "normal" values for each range are represented by the results from a 1998 survey of the general US population (n=6,742) have been included in Table F-19.

At the time of entry into this study (baseline), the group of subjects generally had lower than "normal" mean values and Standard Error of the Mean (SE) reported for all scales, especially for Role Physical (38.5 ± 4.5 (SE)), and Vitality (44.5 ± 2.3(SE)) which were substantially lower than normal (Table F-19). Means for the other six scales ranged from 60.7 (General Health) to 73.9 (Mental Health). Except for Mental Health, the mean scores summarized in Table F-20 clearly illustrate the

compromised quality of life of these subjects, as all means score values were below the mean score values for the general US population. Only three average scores exceeded 70, i.e., Physical Functioning (71.5), Social Functioning (70.7), and Mental Health (73.9), and mean values for Vitality and Role Physical were very depressed. The depressed scores for Role Physical and for Vitality are consistent with the high percentages of those reporting at least moderately severe symptoms, particularly for 'shortness of breath' and 'fatigue' (Table F-17, Arrhythmia Symptoms).

A more detailed description of each of the "domains" of this instrument is presented in Appendix V-1.

Table F-19, Baseline SF-36 Domain Scores [a]

SF-36 Scale	General US Population Scores [c]		REVELATION Tx Study Baseline (n=87-91 [b])		
	Mean	SD	Mean	SE	Median
Physical Functioning	84.2	23.3	71.5	2.7	77.5
Role Physical	80.9	34.0	38.5	4.5	25.0
Role Emotional	81.3	33.0	64.8	4.2	66.7
Bodily Pain	75.2	23.7	69.0	2.5	72.0
General Health	71.9	20.3	60.7	2.3	60.0
Vitality	60.9	20.9	44.5	2.3	45.0
Social Functioning	83.3	22.7	70.7	2.8	75.0
Mental Health	74.7	18.1	73.9	1.9	76.0

[a] Scaled 0 (worst possible) to 100 (best possible)

[b] Indicates the range of response sample sizes for the individual eight domains. Not all subjects completed all questions and five subjects did not complete a baseline questionnaire.

[c] n=6,742 (www.SF36.com), US Population Norms, 1998.

As noted, the mean scores for the general population versus the study population that is the subject of this PMAA show dramatic differences at baseline, particularly in the category (domain) of "Role Physical" and "Vitality". Figure F-5 presents graphic illustrations of these differences.

Atrial Fibrillation Severity Scale

The Atrial Fibrillation Severity Scale (AFSS) is designed for the evaluation of the Severity (and incidence) of Atrial Fibrillation Symptoms[7]. The original ranges of the three characteristics of arrhythmic episodes are 11-point (frequency), 8 point (duration), and 10-point (severity) scales. For ease of interpretation, and to place them in the same range as the SF-36 domain scales, all three measures were transformed to 100-point scales with 100 indicating best possible and 0 indicating worst possible. The total AFSS score is the simple algebraic sum of the original three scale values transformed to a 100-point scale value. Thus, all three scales and the combined scale are constructed such that higher values indicate better status, and increases over time indicate improvements.

The subjects enrolled in this study reported results that can be generally characterized at baseline as having rather frequent arrhythmic episodes (mean =30.1, SE=2.0) of moderate duration (mean = 38.0, SE=2.6) and medium severity (mean = 49.1, SE=2.6), as illustrated in Table F-20. Based on the results summarized in Table F-20, episode frequency perhaps was more troublesome than duration or severity. Overall, these low mean scores generally corroborate the compromised quality of life of these subjects expressed in the SF-36 results at baseline. The mean total AFSS score prior to treatment, 36.0 (SE=1.5), suggests ample opportunity for improvement among these subjects.

Table F-20, Baseline AFSS and Component Scores[a] (n=88-89[b])

Score	Mean	SE	Median
Episode Frequency	30.1	2.0	30.0
Episode Duration	38.0	2.6	42.9
Episode Severity	49.1	2.6	55.6
Total AFSS	36.0	1.5	35.7

[a] Scaled 0 (worst possible) to 100 (best possible)

[b] Indicates the range of sample sizes for the four scores of the table. Not all subjects completed all questions and four subjects did not submit the baseline questionnaire.

7.5 Protocol Procedural Features and Results

7.5.1 Procedural Characteristics

More than one-half of the 98 procedures among these 95 subjects (53/98, 54.1%) involved subjects in normal sinus rhythm, and in approximately 30% (29/98, 29.6%) of the procedures the subjects were noted to be in atrial fibrillation (Table F-21). Cardioversion was performed during the procedure in 41 cases (41.8%). Two (2) of these subjects could not be converted and the decision was made to proceed on ethical grounds. Those two are reported here as protocol deviations. During the procedure the type of sedation was almost evenly split between conscious sedation and general anesthesia with intubation. In all but one procedure the sheath insertion site was the femoral vein.

Table F-21 - Procedural Characteristics (n=98)

Description	Frequency	%
Baseline EKG:		
Normal Sinus Rhythm	53	54.1
Atrial Fibrillation	29	29.6
Other	16	16.3
Total	98 [a]	100.0
Cardioversion		
No	57	58.2
Yes	41	41.8
Total	98 [a]	100.0
Sheath Insertion Site		
Femoral	97	98.9
Jugular	1	1.1
Other	0	0.0
Total	98 [a]	100.0
Type of Sedation		
Conscious	46	51.7
General with intubation	41	46.1
General without intubation	2	2.2
Total	89 [b]	100.0

[a] Number of procedures, 3 subjects were treated with a second procedure

[b] Sedation data not entered for 9 procedures

7.5.2 Procedure Times

The time to complete the RF ablation procedure ranged from 100 minutes to 755 minutes, however, the median total procedure time was 227 minutes, or about 3.8 hours Table F-29). These results illustrate individual differences and, in some cases, a learning curve with related technology, since varying guiding/imaging technologies were used during these procedures. The total procedure time averaged approximately four and one-third hours (262 minutes ± 128 minutes).

The catheterization times for the REVELATION® Tx Microcatheter system and total fluoroscopy times are also reported in Table F-22. These times averaged 192 minutes and ranged from 13 to 475 minutes with a median time of 169 minutes. Fluoroscopy times averaged less than one hour (48 minutes ± 49 minutes) with a range of 2 to 265 minutes and a median time of 32 minutes.

Table F-22 – REVELATION® Tx Microcatheter System Catheterization and Fluoroscopy Times (minutes) (n=96-98 [a])

Total Time	min	max	median	mean ± SD
REVELATION® System Time	13	475	169	192 ± 89
Fluoroscopy Time	2	265	32	48 ± 49
Procedural time	100	755	227	262 ± 128

[a] In dicates the range of sample sizes for each of the three individual time measurements

A separate listing of total procedure times, investigational device procedure time and total fluoroscopy times (including minimum and maximum) by investigational site is presented in Table F-56 in Appendix F-1.

7.5.3 Procedural Success Endpoint

The protocol defines procedural (acute) success as a reduction in electrogram amplitudes at the line(s) of ablation post-ablation compared to pre-ablation. Three indicators represent such changes: a) reduction in the amplitude, fragmentation or widening of local electrograms; b) the appearance of split potentials; or, c) an increase in pacing thresholds.

Because measurement of pacing thresholds may compromise and/or complicate patient care through increased procedure times, (especially fluoroscopy) and because the increase in pacing thresholds in Phase IIa and initial Phase IIb subjects was shown to be statistically significant ($p<0.01$) measurement of pacing thresholds was discontinued for Phase III. Table F-23 summarizes the data that were submitted to FDA reporting these results in a progress report for Phase IIa, for the results from the first five study subjects (Supplement 7 dated August 3, 1998).

Table F-23
Procedural Pacing Threshold and Electrogram Amplitude
Pre- and Post-Ablation (n=5)

Subject #	Pacing Threshold (mA)			
	Number of paired values	Mean pre	Mean post	% change
0101^	4	2.75	5.50	100
0301	21	4.32	8.08	87
0302	14	4.02	8.14	102
0303	26	5.57	9.72	75
0304	22	7.69	9.98	30
Mean‡ ± SE		5.23 ± 0.34	8.94 ± 0.21†	72

† $p < 0.01$ post- vs. pre-ablation

‡ Mean calculated from population data. Mean % change calculated as weighted average.

^ Paired pacing thresholds are available for Line B (septal) only. Subject 0101 developed atrial fibrillation/atrial flutter following delivery of radiofrequency energy along Line A (posterolateral IVC-SVC) and Line D (anterior SVC-TA).

Evaluating changes in electrogram amplitude values pre and post ablation as a means of measuring procedural (acute) effectiveness in the treatment of atrial fibrillation has some significant drawbacks that must be considered in this discussion.

Conventional endocardial ablation catheters ablate with a single electrode to treat a very different arrhythmia that, when effectively ablated, will generate a visibly different electrogram.

With the REVELATION® Tx multielectrode catheter that delivers RF energy through eight (8) electrodes to create a lesion of approximately 6.0 cm in length, a decision must be made where along this length to measure amplitude changes. Consistent measurement of these values requires the doctor to perform that measurement at least four times for each lesion, or eight or sixteen times if he or she decides to repeat the series of burns from all eight electrodes. Furthermore, each measurement should align the pre-ablation measurement location with post-ablation measurement location, which is a significant challenge in a beating heart. This requirement was perhaps the single most difficult protocol requirement for the investigators to comply with and the accumulated data reflect that difficulty.

Data are available for a subset of the possible data points for this evaluation. These data represent those pairs of values that appear to be taken from the same electrode both pre and post ablation. There were many other data points but they were not paired at the same electrode and so were not included in this analysis. In addition, there are occurrences of post ablation amplitude being higher than the corresponding pre-ablation amplitude, which is an indicator not of lesion success or failure, but of catheter movement from pre- to post-ablation measurement, since it is not possible to create a higher amplitude by ablation.

Table F-24 summarizes the extent to which amplitude reduction could be measured by all available pre and post ablation corresponding pairs of values per procedure. They are presented here by lesion type based on the 98 patient procedures included in this study. It must be noted that bi-directional block is the primary indicator of procedural success for the isthmus line, so there are far fewer data points for this

lesion than the others. Similarly, the anterior lesion, seldom used, reflects matching pairs of electrogram amplitude measurements from two patient procedures.

Table F-24, Electrogram Amplitude Reduction (n=98 patient procedures)

Lesion Location	# Procedures	Mean Pre	Mean Post	Mean % Reduction	SD	Min	max
Postero-septal	52	1.43	0.87	23.1	30.2	-58.8	78.9
Postero-lateral	52	1.33	0.95	13.2	79.9	-476	69.9
Isthmus	16	0.72	0.37	29.6	29.4	-16.7	67.4
Anterior	2	0.52	0.47	4.0	10.2	-3.2	11.2

It is also important to note that acute, procedural success as depicted here does not reflect the chronic success seen in the follow up of the study subjects. That is, if one accepts that a reduction in post ablation amplitude of ≥50% is an indication of clinical success based upon the potential for transumrality[8] and that transumrality is an indicator for clinical success, this correlation is not confirmed by the clinical success of the patients. Gaita also reports that he uses the presence of a decrease in amplitude as an indicator of a reduction in local electrical atrial signal, although it is not quantified[9].

It should be acknowledged that the 98 patient procedures summarized above may not be representative of the procedural results, since these particular data were not consistently recorded for each electrode pair that delivered RF energy during the lesion creation. If at least one set of paired electrogram measurements were recorded for each line, there would be approximately 290 records (98 procedures times 3 lines, with some patients receiving lesion sets with 2 lines and some with 4 lines).

Therefore, it is not advisable to draw conclusions from these data regarding procedural success.

7.5.4 Conductivity

The ranges, mean values, and standard deviations for A-H and H-V intervals are quite similar pre and post ablation, indicating no apparent clinical effect of treatment on these parameters (Table F-25).

Table F-25 - Pre and Post Ablation A-H H-V Intervals (n=69-71 [a])

Total Time	Min	Max	Mean ± SD
Pre-Ablation A-H interval (msec)	39	208	96 ± 33
Pre-Ablation H-V interval (msec)	28	129	52 ± 17
Post-Ablation A-H interval (msec)	34	196	93 ± 31
Post-Ablation H-V interval (msec)	30	105	55 ± 15

[a] Indicates the range of sample sizes for the four time parameters. Values not recorded for all subjects at all procedures

7.6 Follow up outcomes

7.6.1 NYHA Status

There was relatively little change in NYHA class from baseline in these subjects, as illustrated in Table F-26. There was an increase in the percentage of subjects in Class I from baseline (77.4%) to six months (85.9), but two subjects were noted to be NYHA Class III at six months whereas none was at the level at baseline. One of those subjects [redacted] entered the study with congestive heart failure that continued to worsen and the other [redacted] subject is an insulin dependent diabetic with fluid volume overload in response to Diovan therapy.

Table F-26 - NYHA Class

Class	Definition	Pre-Ablation		3 Months Post-Ablation		6 Months Post-Ablation	
		freq.	%	freq.	%	freq.	%
I	No limitations of activities: no symptoms from ordinary activity.	72	77.4	67	80.7	67	85.9
II	Slight limitation of activity: comfortable at rest or with slight exertion.	21	22.6	14	16.9	9	11.5
III	Marked limitation of activity: comfortable only at rest.	0	0.0	2	2.4	2	2.6
IV	Confined to a bed or chair; any physical activity brings on discomfort and symptoms also occur at rest.	0	0.0	0	0.0	0	0.0
Total		90 [a]	100.0	83	100.0	78	100.0

[a] NYHA Status data not available for 2 patients.

7.6.2 Cardiac Symptoms

Study subjects are asked to report the presence and severity of any cardiovascular symptoms they have experienced during the previous follow up period. The severity is ranked on a scale of 1 to 5 with 5 being the most severe. For simplicity, only those symptoms ranking '3' or greater (at least "moderate" severity) are reported in Table F-27.

As of each the three and six-month follow up visits, there was at least a 35% reduction in incidence of the five individual common and other miscellaneous arrhythmia symptoms relative to baseline. Notably, there was also at least an approximately 50% reduction in the incidence of shortness of breath, palpitations, lightheadedness, and fatigue relative to baseline at this time. Although the incidence of symptoms was reduced, the relative levels of severity for those symptoms were similar at six months compared to baseline, except for palpitations where the percentage of at least moderate severity dropped from 81.6% to 55.9%.

Table F-27 - Baseline and Six-Month Common Arrhythmia Symptoms

Symptom	Baseline		3 months post-ablation		6 months post-ablation	
	Presence n=95 freq (%)	Severity freq/n (%)[a]	Presence n=83[b] freq (%)	Severity freq/n (%)[a]	Presence n=79[b] freq (%)	Severity freq/n (%)[a]
Chest Pain	19 (20.0)	11/19 (57.9)	9 (10.8)	5/7 (71.4)	10 (12.7)	7/10 (70.0)
Shortness of Breath	46 (48.4)	31/44 (70.4)	21 (25.3)	13/19 (68.4)	17 (21.5)	10/15 (66.7)
Palpitations	85 (89.5)	62/76 (81.6)	45 (54.2)	25/40 (62.5)	35 (44.3)	19/34 (55.9
Lightheadedness	33 (34.7)	24/31 (77.4)	17 (20.5)	11/17 (64.7)	13 (16.5)	10/12 (83.3)
Fatigue	53 (55.8)	37/46 (80.4)	26 (31.3)	18/25 (72.0)	20 (25.3)	15/19 (78.9)
Other	28 (29.5)	19/24 (79.2)	10 (12.5)	7/10 (70.0)	16 (21.3)	9/14 (64.3)
No Symptoms Reported	1 (1.1)	NA	29 (34.9)	NA	29 (36.7)	NA

[a] Some subjects did not report a severity for their symptoms

[b] One subject did not report

7.6.3 Episode Reduction

Effectiveness of treatment as indicated by frequency of symptomatic episodes reported via event monitoring transmissions is evaluated against the change since baseline. Weekly event monitor transmissions are compulsory during month one, month three, and month six, even if the subject does not experience symptomatic episodes. For the convenience of the study subject, continuous transmission from treatment through month three was permitted, even though the protocol required compulsory transmissions for month one and month three. For reference, the

maximum possible sample sizes for each assessment interval are illustrated in Figure F-2, page 27.

As apparent in Table F-28a, there were substantial and highly statistically significant ($p<0.0001$, paired t-test) decreases in the mean number of symptomatic arrhythmic episodes/month at both three months (3.5 ± 5.4) and six months (1.9 ± 2.9) follow up relative to baseline (9.9 ± 9.1).

Table F-28a- Baseline and Follow Up Number of Symptomatic AF Episodes

Number of Episodes	Baseline		3 months		6 months	
	freq	%	freq	%	freq	%
0	-	-	32	38.1	37	46.8
1	-	-	10	11.9	13	16.5
2	-	-	10	11.9	7	8.9
3	14	14.7	2	2.4	8	10.1
4	15	15.8	6	7.1	5	6.3
5	7	7.4	7	8.3	0	0.0
6	9	9.5	2	2.4	1	1.3
7	4	4.2	3	3.6	4	5.1
8	6	6.3	3	3.6	1	1.3
9	9	9.5	2	2.4	0	0.0
10-14	16	16.8	3	3.6	3	3.8
15-19	5	5.3	1	1.2	0	0.0
20-29	6	6.3	2	2.4	0	0.0
30+	4	4.2	1	1.2	0	0.0
Total	**95**	**100.0**	**84**	**100.0**	**79** [b]	**100.0**
Mean, SD	**9.9 ± 9.1**		**3.5** [a] **± 5.4**		**1.9** [a] **± 2.9**	

[a] $p<0.0001$, paired t-test

[b] One subject did not transmit event monitoring data in time for this interval close

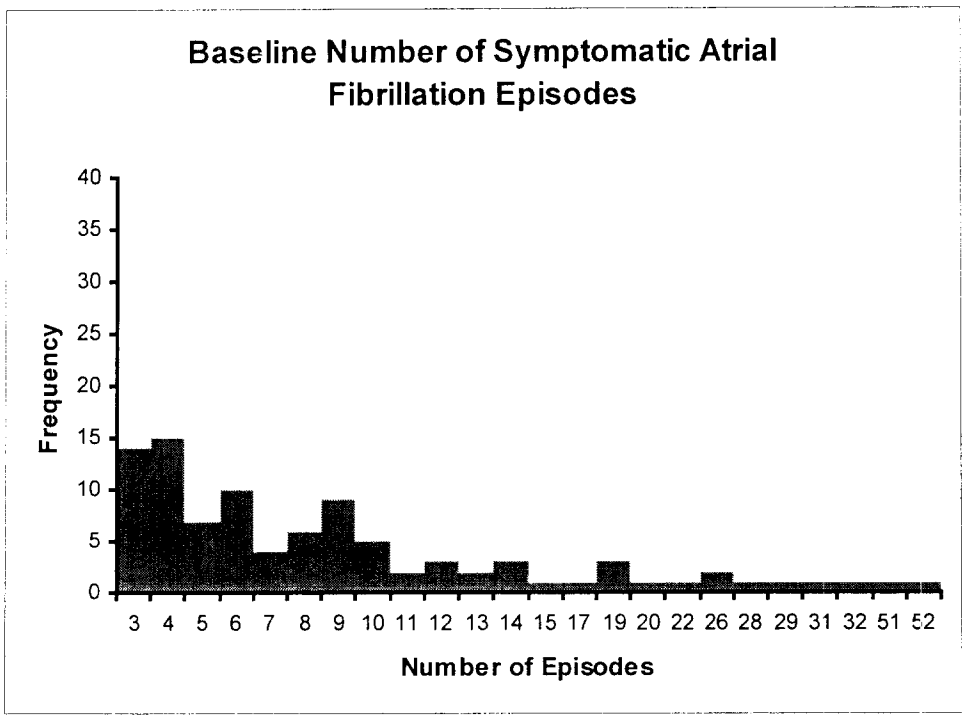


Figure F-5, Baseline Number of Symptomatic Atrial Fibrillation Episodes (n=95)

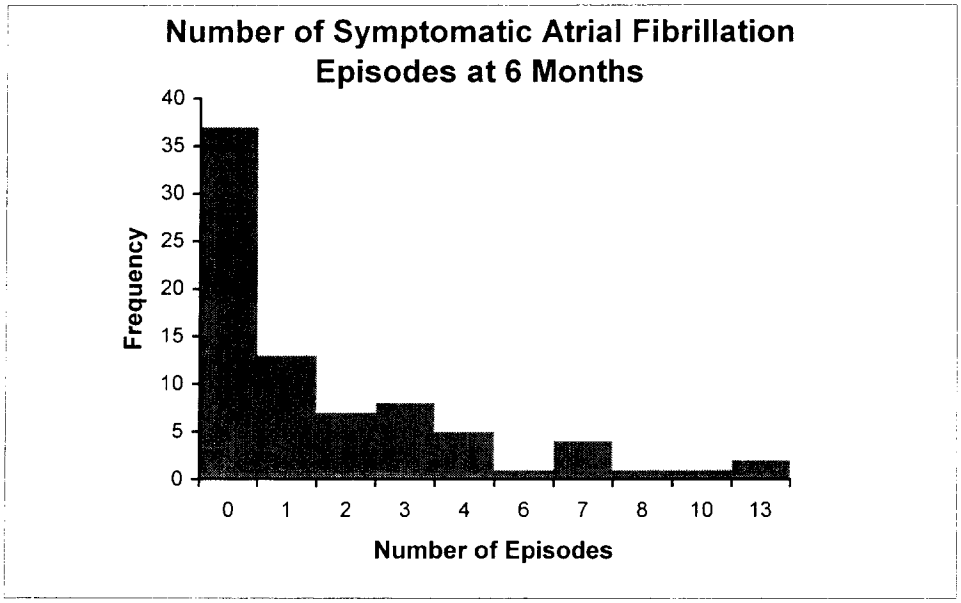


Figure F-6, Distribution of 6-Month Post-Ablation Episodes by Frequency (n=79)

During the month of episode monitoring at baseline, all qualified subjects had at least three symptomatic episodes. Upon follow up after RF ablation treatment, more than half the subjects (52/84, 61.9%) at three months and more than three quarters (57/79, 72.2%) of the subjects at six months had fewer than three symptomatic episodes per month. It is also noteworthy that prior to treatment approximately one-third of the subjects (31/95, 32.6%) had at least ten or more symptomatic episodes per month, but at six months only three subjects (3/79, 3.8%) had at least ten symptomatic episodes.

There were five patients for whom the baseline number of symptomatic episodes was disputed due to differing interpretations of the transmitted strips. In three of those cases, a third, independent cardiologist's interpretation yielded different results than the first two, failing to resolve the dispute. In two of those cases, the original data were lost in a computer failure at the contract event monitoring service facility and could not be retrieved and referred for further interpretation.

In all five cases, the investigators felt that it was in the best interests of the patients to proceed with the treatment. In three of those cases, the fact that the number of symptomatic episodes was disputed was not reported until after the patients had undergone treatment.

In all five cases the subjects have been included in the study and followed as regular study subjects. However, because of the disputed baseline numbers, the evaluation of clinical success and failure as indicated by episode frequency has been calculated both with (Table F-28a) and without (Table F-28b) the results for these five subjects.

Table F-28b, Baseline and Follow Up Number of Symptomatic AF Episodes

Number of Episodes	Baseline		3 months		6 months	
	freq	%	freq	%	freq	%
0	-	-	29	36.7	33	44.6
1	-	-	10	12.7	13	17.6
2	-	-	8	10.1	7	9.5

3	14	15.6	2	2.5	7	9.5
4	14	15.6	6	7.6	5	6.8
5	7	7.8	7	8.9	0	0.0
6	8	8.9	2	2.5	1	1.3
7	4	4.4	3	3.8	4	5.4
8	6	6.7	3	3.8	1	1.3
9	8	8.9	2	2.5	0	0.0
10-14	16	17.8	3	3.8	3	3.0
15-19	5	5.6	1	1.3	0	0.0
20-29	4	4.4	2	2.5	0	0.0
30+	4	4.4	0	0.0	0	0.0
Total	**90**	**100.0**	**79**	**100.0**	**74** [b]	**100.0**
Mean, SD	**9.6 ± 8.9**		**3.7** [c] **± 5.5**		**2.0** [c] **± 2.9**	

[a] Statistics do not include five subjects with disputed numbers of baseline episodes.

[b] One subject did not transmit event monitoring data in time for this interval close

[c] $p<0.0001$, paired t-test

Exclusion of these subjects' results does not materially affect the conclusions drawn from Table F-28a, or from the following Table F-29a. Figure F-7 graphically depicts the similarities in the results between the two groups.

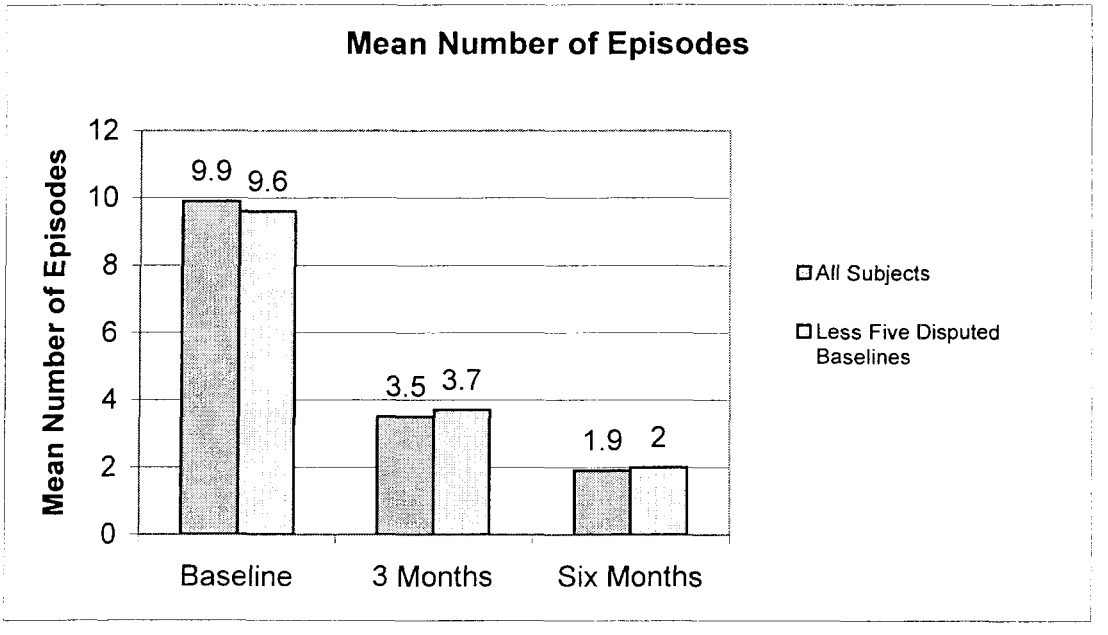


Figure F-7, Mean Number of Episodes

Based on the baseline and follow-up symptomatic episode data whose results are summarized in Tables F-28a, b and the individual computed percentage reductions per subject, the statistical information of Table F-29a, and Table F-29b was derived.

Patient treatment success, as defined by at least a 50% reduction in the number of symptomatic episodes per month for baseline episodes five or greater (≥5) and 75% for baseline episodes 3-4, was achieved in over two thirds of the study subjects at three months (57/84, 67.9% Table F-29a) and in over three-fourths (67/79, 84.8%) of the subjects at six months. The 95% confidence intervals for the success rates at three and six months are (57.3%, 76.9%) and (75.3%, 91.1%), respectively.

Almost all of the subjects (72/79, 91.1%) had at least some reduction in number of symptomatic episodes at six months, and nearly half of the subjects (37/79, 46.8%) had no symptomatic episodes during this monitoring month.

Table F-29a - Percent Reduction in Arrhythmia Episodes

Criterion	3 Month (n=84) freq/n (%)	6 Month (n=79[d]) freq/n (%)
# of subjects with Episode Reduction compared to Baseline	74/84 (88.1)	72/79 (91.1)
≥50% Reduction [a]	57/84 (67.9)	67/79 (84.8)
100% Reduction [c]	32/84 (38.1)	37/79 (46.8)
<50% Reduction [c]	27/84 (32.1)[c]	12/79 (15.2)[c]
No Reduction	10/84 (11.9)	7/79 (8.9)
Withdrew	2/84 (2.4)	7
Non-Compliant (event monitor)	4	1
Patient not yet at 3, 6 months	9	12
Data not in database at cut-off date	4	0
Mean % reduction ± SE	59.5 [b, d] ± 6.4	74.7 [b, d] ± 4.9

[a] ≥75% for 3-4 baseline episodes

[b] p<0.0001, paired t-test

[c] Includes those with "no reduction" as a subset of the <50% reduction group. In the >50% reduction group, those with 100% reduction are included..

[d] One subject did not transmit event monitoring data in time for this interval close

The overall mean percentages of reduction in symptomatic episodes were 59.5% and 74.7% for the three and six month monitoring interval, respectively. The 95% confidence intervals for these mean episode percentage reductions at three and six months are (47.0%, 72.0%) and (65.1%, 84.3%), respectively.

These results are not materially different when the five patients with disputed baseline episodes are incorporated into the calculations, as illustrated in Table 29b.

Table F-29b - Percent Reduction in Arrhythmia Episodes

Criterion	3 Month (n=79) freq./n (%)	6 Month (n=74 [d]) freq./n (%)
# of subjects with Episode Reduction compared to Baseline	69/79 (87.4)	67/74 (90.5)
≥50% Reduction [a, c]	53/79 (67.1)	62/74 (83.8)
100% Reduction	29/79 (36.7)	33/74 (44.6)
<50% Reduction [c]	26/79 (32.9 [c])	12/74 (16.2 [c])
No Reduction	10/79 (12.6)	7/74 (9.5)
Withdrew	2	7
Non-Compliant (event monitor)	4	1
Patient not yet at 3, 6 months	9	12
Data not in database at cut-off date	4	0
Mean % reduction ± SE	58.0 [b] ± 6.7	73.6 [b, d] ± 5.2

[a] ≥75% for 3-4 baseline episodes [b] $p<0.0001$

[b] Statistics do not include five subjects with disputed numbers of baseline episodes.

[c] Includes those with "no reduction" as a subset of the <50% reduction group. In the >50% reduction group, those with 100% reduction are included.

[d] One subject did not transmit event monitoring data in time for this interval close

In conclusion, treatment with the REVELATION® Ablation System has been shown to be highly effective in reducing symptomatic episodes in this patient population.

7.6.4 Antiarrhythmic Therapy Requirements

Methodology:

All subjects in this study were required by an inclusion criterion to be refractory to at least two (2) antiarrhythmic drugs (AADs), unless one drug to which the subject was refractory was Amiodarone, then Amiodarone alone would qualify the subject as eligible.

Data were collected at baseline to document the drugs to which the study subject was refractory. At each follow up visit, any change in type of dosage of AADs was recorded. For each change, the investigator was asked to report whether the stated change represented an increase or a decrease in AAD therapy.

In performing the analysis of these data, an independent pharmacist was asked to review the results reported for each subject at each assessment interval and determine if the AAD use reported represented an increase, decrease, or no change since baseline based upon the type and dosage and combination of AADs reported. The pharmacist was blinded to baseline and follow up episode reduction outcomes. The pharmacist's report was the source of the subject data used for the following analyses. A copy of the pharmacist's report is included in Appendix V-1.

Results

The use of antiarrhythmic drugs (AADs) in these drug refractory patients remained unchanged or was reduced following ablation by the sixth month, with 59/80, 73.8% demonstrating either a decrease or remaining on the same level of drug that had been ineffective before treatment. These results are illustrated in Table F-30.

Table F-30, Change in AAD Use from Baseline to Six Months (n=80)

Change	Frequency	%
Decrease	33	41.3
No Change	26	32.5
Increase	21	26.2
Total	80	100.0

To evaluate whether the results of episode reduction might be related to changes in AAD use, treatment success/failure for those subject who completed the six-month assessment interval were stratified by AAD use at six months compared to baseline use. The results are summarized in Table F-31.

Table F-31 Six-Month Episode Outcome by AAD Results

AAD use	Failure (<50% Reduction in Episodes)		Success (≥50% Reduction in Episodes)		Total	
	Freq	%	Freq	%	Freq	%
Decrease	2	6.9	27	93.1	29	100.0
No Change	7	26.9	19	73.1	26	100.0
Increase	3	15.8	16	84.2	19	100.0
Total	12	16.2	62	83.8	74	100.0

*Excludes the five patients with disputed baseline episodes

The group of subjects with decreased AAD use at six months showed the highest success rate (93.1%, Table F-31), with the group of subjects with increased AAD use at six months having the next highest success rate. The groups with decreased and increased AAD use also had similar levels of mean percentage episode reduction, i.e., 77.6% and 80.2%, respectively (Table F-32).

Table F-32, Episode Reduction (%) at Six Months by AAD status

AAD use	Mean % Episode Reduction	SD	min	max
Decrease	77.6	48.9	-160*	100
No Change	64.3	50.3	62	100
Increase	80.2	27.2	0	100
Total	73.6	44.9	-160	100

* indicates more episodes at six months than baseline

These results do not indicate any discernable association between changes in AAD use and episode outcome and mean reduction and, therefore, no bias from the influence of AAD use can be inferred.

7.6.5 Hospitalizations and Emergency Room Visits

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

Table F-33 – Number of Subjects with Emergency Room Visits and Hospitalizations Related to Atrial Fibrillation During the 24 Months Post-procedure

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

7.6.6 Quality of Life

SF-36

The descriptive statistics for the eight domains of the SF-36 general quality of life instrument are provided in Table F-34 and Figure F-7. The three-month mean values showed overall improvements in quality of life for each of the eight scales. There were noteworthy and significant ($p<0.05$, paired t-test) improvements for six of the eight mean values at this time, i.e., Physical Functioning ($p<0.001$), Role Physical ($p<0.0001$), Role Emotional ($p<0.05$), Bodily Pain ($p<0.01$), Vitality ($p<0.0001$), and Social Functioning ($p<0.001$). The largest improvements among these scales were for Role Physical where the baseline mean value improved from 38.5 to 60.7, for Role Emotional, whose baseline mean value improved from 64.8 to 77.3, and for Vitality, whose baseline mean value improved from 44.5 to 55.3. In addition to being highly statistically significant, all of these improvements are also considered to be clinically significant in magnitude (i.e., >10 points change).

Table F-34 - Baseline and Follow Up SF-36 Scale

SF-36 Scale	General US Population Scores [e]		Baseline (n=86-90 [f])		Three Month (n=75-78 [f])		Six Month (n=71-75[f])	
	Mean	SD	Mean	SE	Mean	SE	Mean	SE
Physical Functioning	84.2	23.3	71.5	2.7	78. 3[b]	2.7	79.4[c]	2.7
Role Physical	80.9	34.0	38.5	4.5	60.7[a]	4.9	58.8[a]	4.9
Role Emotional	81.3	33.0	64.8	4.2	77.3[d]	4.0	74.9	4.6
Bodily Pain	75.2	23.7	69.0	2.5	75.7[c]	2.8	76.1[d]	2.9
General Health	71.9	20.3	60.7	2.3	61.8	2.3	61.2	2.4
Vitality	60.9	20.9	44.5	2.3	55.3[a]	2.5	54.7[a]	2.7
Social Functioning	83.3	22.7	70.7	2.8	79.7[b]	2.8	82.1[a]	2.7
Mental Health	74.7	18.1	73.9	1.9	76.7	1.8	76.4	2.0

[a] $p<0.0001$ by paired t-test, [b] $p<0.001$ by paired t-test, [c] $p<0.01$ by paired t-test, [d] $p<0.05$ by paired t-test

[e] The general population was sampled to acquire normative values for these domains (n=6,742 – see also Table F-19, page 67).

[f] Indicates the range of response sample sizes for each of the eight domains.

These subjects also demonstrated substantial and consistent improvement in quality of life at the six-month follow up visit. Compared to baseline, mean values for all eight scales also showed improvement at this follow up visit assessment. Mean values for two of the domains at six months, General Health and Mental Health, were relatively little improved from baseline, but except for Role Emotional, means values for the other six domains were significantly higher at six months. The largest clinically significant (>10 points) improvements in mean values were for Role Physical ($p<0.0001$), as average values increased 50% over baseline (38.5 to 58.8); Vitality ($p<0.0001$), as mean values improved from 44.5 to 54.7 over this period; and Social Functioning ($p<0.001$), with values improving from 70.7 to 82.1. There was also an essentially clinically significant improvement for Role Emotional, whose baseline mean value improved from 64.8 to 74.9, that did not quite achieve statistical significance ($p=0.06$). Figure F-8 presents a graphic illustration of these results.

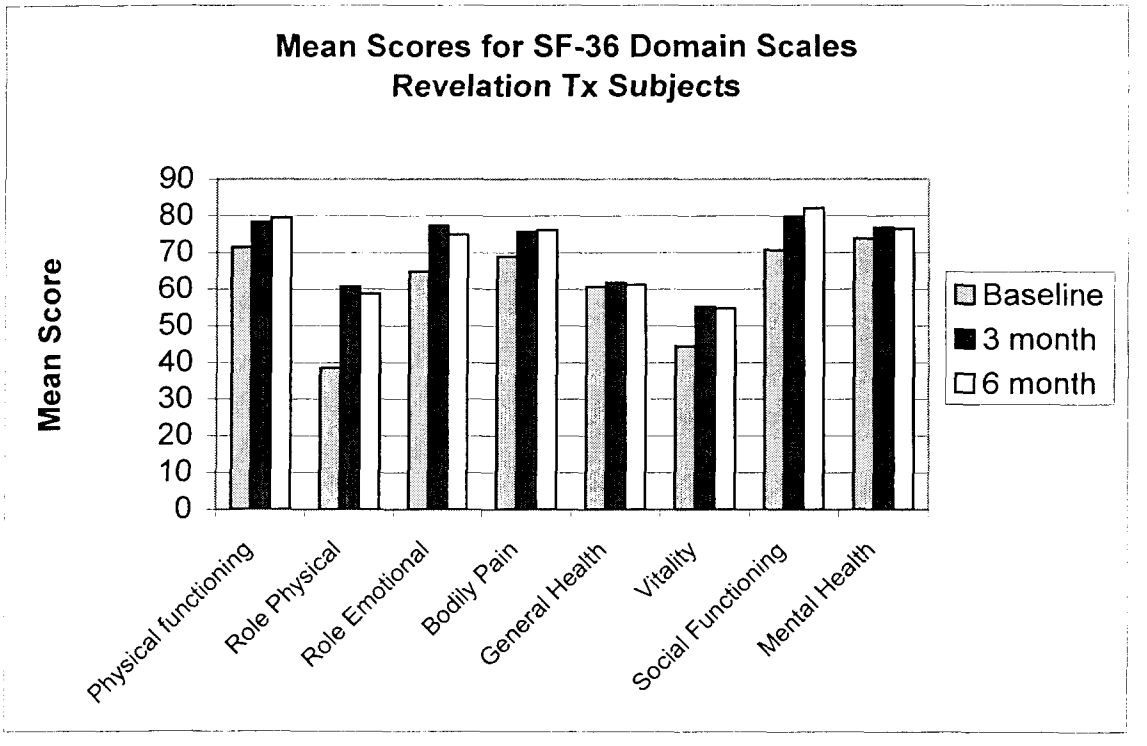


Figure F-8, SF 36 Outcomes by Domain and Assessment Interval

In conclusion, these subjects demonstrated improvement in all eight SF-36 quality of life scales at both the three and six month follow up assessments. There were quite substantial and clinically significant and highly statistically significant improvements for Role Physical, Role Emotional, Vitality, and Social Functioning at both of these follow up assessments, clearly indicating overall substantial patient benefit.

Atrial Fibrillation Severity Scale (AFSS)

The results displayed in Table F-35 demonstrate significant improvement for all episode parameters at three months after treatment. The mean score for Episode Frequency improved substantially, from 29.8 to 45.4, a highly statistically significant improvement ($p<0.001$). Episodes at this time were generally significantly shorter in duration ($p<0.001$), and significantly less severe ($p<0.001$). Improvements in mean scores for these three parameters were reflected in the total AFSS score, which improved approximately one-third over baseline ($p<0.001$).

Table F-35 - Baseline and Follow Up AFSS and Component Scores[a]

Score	Baseline (n=88-89 [e])		Three Month (n=66-72 [e])		Six Month (n=60-70 [e])	
	Mean	SE	Mean	SE	Mean	SE
Episode Frequency	30.1	2.0	45.4 [a]	3.0	49.7 [a]	3.2
Episode Duration	38.0	2.6	49.0 [b]	3.7	49.8 [c]	4.3
Episode Severity	49.1	2.6	66.9 [a]	3.1	67.1 [a]	3.4
Total AFSS	36.0	1.5	47.8 [a]	2.1	50.8 [a]	2.4

[a] $p<0.0001$ by paired t-test, [b] $p<0.001$ by paired t-test, [c] $p<0.01$ by paired t-test, [d] $p<0.05$ by paired t-test

[e] Indicates the range of response sample sizes for each of the four domains.

Mean score values for all three parameters were also substantially higher at six months after treatment, as was the mean total AFSS score. The six-month mean values were 49.7, 49.8, 67.1, and 50.8 for Episode Frequency ($p<0.001$), Episode Duration ($p<0.01$), Episode Severity ($p<0.001$), and total AFSS ($p<0.001$), respectively.

Thus, these results for the total and component AFSS scores indicate overall substantial and statistically significant patient benefit during the six months after treatment with the REVELATION Tx Ablation System in terms of general improvement in episode frequency, duration, and severity. Figure F-9 presents a graphic illustration of these results.

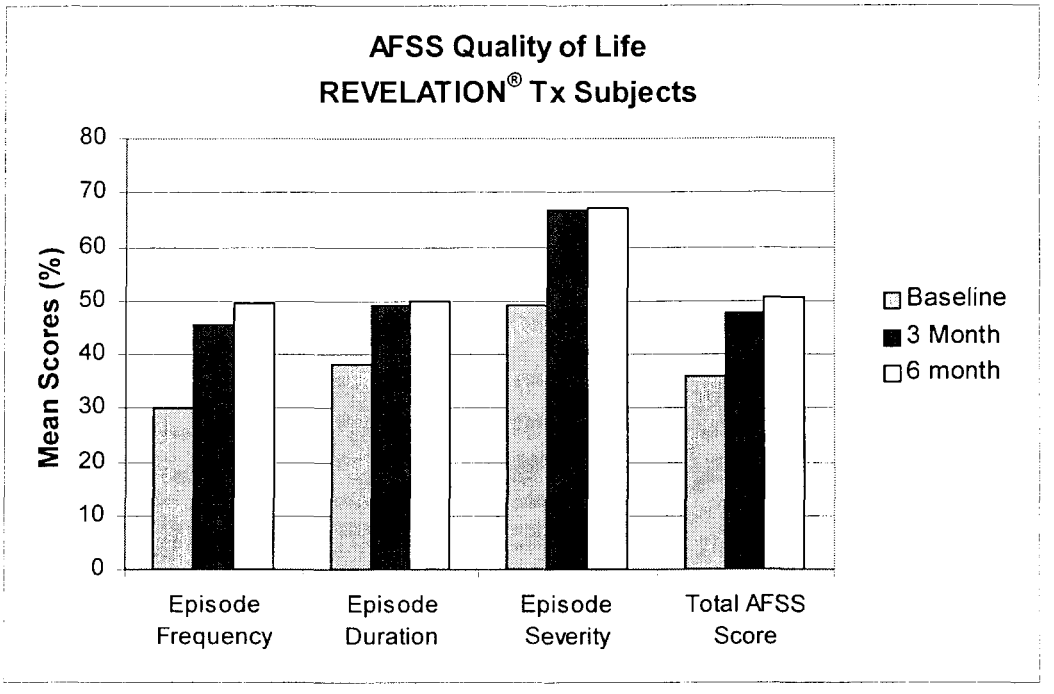


Figure F-9, Atrial Fibrillation Severity Scale Improvement Over Time

7.6.7 Complications

All Adverse Events experienced by study subjects were documented and are reported in this submission. Adverse Events were defined by the protocol (see Appendix V-1) as a series of potential complications that could be expected in a cardiac catheterization. Sites were required to make a determination of whether the event was related to the device or the procedure (or not related). That determination could be "probably", possibly" or "not related". Occurrences of adverse events are reported here within these categories, as determined by the site (investigator).

An Adverse Event could be a Major Complication if it met certain criteria for acute severity. Major Complications are defined by FDA as those adverse events that occur within the first 7 days post procedure and are either life threatening, require major intervention (including new hospitalization or extended hospital stay) to resolve; or leave permanent or significant transient impairment of a body part or function.

Major Complications are presented in Table F-36.

There were four (4) "major complications" reported for these 95 patients with 98 procedures (4/98), for a 4.1% major complication rate. None of these complications is unanticipated and each was referenced in the protocol and informed consent documents. These complications include a pericardial effusion, an SA node dysfunction, a stroke, and an AV fistula. The details of each of these complications are provided in the following pages.

In addition, any other significant complication that is reported to be 'likely related' to the procedure or the device is reported in Table F-37.

A complete listing of all reported adverse events (AEs) that are reported to be possibly or probably related to the device or the procedure is presented in Table F-38. A listing of all reported AEs without regard to their relationship to the device or procedure, is presented in Table __, Appendix V-1.

A total of 57 complications of any type have been reported by subjects in this study as of the report date and determined by the investigational site to be possibly or probably related to the device or the procedure. Most complications (49/57, 85.9%) were reported to be related to the procedure. However, of the eight complications reported to have a possible or uncertain relationship to the device, two are events occurring more than 100 days post-ablation and a third is a drug reaction four days post procedure.

There have been no un-anticipated complications and the reported complications are considered to be a reasonable safety profile for this population group.

7.6.8 Data Safety Monitoring Board

Cardima created a Data Safety Monitoring Board (DSMB) for the purpose of reviewing interim data for its significance regarding the safety of the study subject and regarding the conformance of the data collection activities to the stated study objectives. The DSMB included a cardiologist, an EP cardiologist and a biostatistician.

The DSMG convened three times, twice by teleconference, to review distributed data, including an annual progress report submitted to FDA, for possible issues relevant to safety data.

At no time did the DSMB indicate a concern about the safety of the study subjects or about the data resulting from the study at the given intervals.

The last conversation was a teleconference to discuss the most recent complications and the preparation for the submission of the PMA. At that time, as each prior meeting, the Chairman of the DSMB reported the complications seen to date suggest a reasonable and acceptable safety profile.

Table F-36 Major Complications (*Occurring Within 7 Days Of Procedure with Significant Intervention)*

Pt ID	Pt Initial	Compli-cation	Abla-tion Date	Onset Date	Resolve Date	Description	Reported Relation-ship
		Pericardial effusion with arrhythmias	1/10/02	1/10/02	1/14/02 & 1/21/02	Pt. symptomatic 2 hrs post procedure with nausea, hypotension. Echo showed small pericardial effusion treated initially with dopamine and later, when symptoms did not resolve, pericardial window created to drain. AF self-terminated and pt. discharged home in NSR. Dr. believes protocol requires maintaining ACT too high and that is cause of effusion.	Probably Procedure-Related
		Sinus Node Injury Requiring Pacemaker Implantation	10/24/01	10/25/01	10/31/01	Post procedural complications included aspiration pneumonia, anxiety attacks, self-limited Pericarditis and skin burns, all of which resolved quickly with appropriate therapies. Pt. continued to experience AF with SA Dysfunction that "likely arose from lateral lesions near SA Node. SA dysfunction continued for >1 week and was treated with PPM/ICD implant and discharged home.	Probably Procedure Related
		Stroke	2/4/00 12/99	2/5/00	7/31/00	Pt. presented with symptoms of neurologic deficit on 2/5/00 following 2nd Cardima procedure. A CT scan demonstrated suggestion of a left middle cerebral artery embolic infarct. Bi-directional block at isthmus was no longer "durable" and extensive lesions were delivered at the isthmus until durable block was demonstrated. During procedure evidence of previously undetected PFO was noted. Patient stabilized as of 7/31/00 and is "fully functional" as of 8/02/02.	Possibly Procedure Related

Table F-36 Major Complications (*Occurring Within 7 Days Of Procedure with Significant Intervention)*

Pt ID	Pt Initial	Compli-cation	Abla-tion Date	Onset Date	Resolve Date	Description	Reported Relation-ship
						Pt. first treated in 12/99 when AF was "fixed" and pt. was hypothyroid probably due to Amiodarone therapy he had been on since late 1994. Pt. also had Protein C deficiency and was on Coumadin for this condition. PV ablation was discussed but ruled out due to history of DVT and pulmonary embolus. Pt. consented to Cardima study and was converted to NSR pre-treatment and successfully ablated on 12/10/99. Bi-directional block at isthmus was documented. Amiodarone continued. Intolerance of Amiodarone prompted a re-visit with Dr. that resulted in this scheduled re-ablation in Cardima study.	
		AV Fistula	4/27/01	4/28/01	5/07/01	Pt. reported mild discomfort in left groin area day after procedure. Duplex US showed femoral AV fistula. Pt. was discharged home in NSR to see if fistula resolved spontaneously. On 5/03, pt. reported sudden worsening of symptoms and was admitted to hospital for successful surgical repair of fistula and was discharged home on 5/7.	Probably Related to Procedure

Table F-37 Other Significant Complications *(Occurring Within 7 Days of Procedure)*

Pt ID	Pt Initial	Compli-cation	Abla-tion Date	Onset Date	Resolve Date	Description	Reported Relation-ship
		Syncope	2/21/01	2/28/01	5/16/01	Post procedural syncope with 2.4 second pauses. AAD Rx was reduced and pauses subsided without further intervention.	Probably related to Procedure
		Prolonged Hospitalization due to Tikosyn Cardioversion	12/18/01	12/19/01	5/06/02	Dr. initiated Tikosyn protocol to control AF precipitated during ablation procedure. "Standard of care" with Tikosyn protocol requires three-day hospitalization to monitor for long QT intervals. Pt. discharged on 12/22/01. Dr. believes the recurrent AF is the result of exacerbated cardiac condition, not procedure or device.	Not Related to either device or procedure
		Sinus Node Dysfunction	4/03/01	4/04/01	4/04/01	Pt. had pre-existing tachy-brady syndrome. Dr. believes ablation catheter was not near sinus node during RF delivery and thus did not cause junctional rhythm. Pt. was in AF during most of procedure so junctional rhythm not seen until AF spontaneously terminated several hours after the procedure. Pacemaker was implanted following the procedure.	Not Related to either device or procedure
Occurring >7 Days After Procedure							
		Stroke	6/06/00	7/12/00	11/27/00	Successful ablation and discharged home in NSR. Site reports findings of carotid atheromatous plaques bilaterally and evidence of possible ischemic infarct with further evidence of subacute left middle cerebral artery distribution infarct. Site also notes that pre-ablation TEE showed small blood clot not reported at the time of the TEE.	Uncertain Relationship to Procedure

Table F-38,* Alphabetical Listing of All Complications Possibly or Probably Related to Procedure or Device (or with "Uncertain" Relationship)

#	Study	Pt ID	AE Symptom	Severity	Rel To Device	Rel To Proc	Date Of Onset	Stop Date	Tx Date	PPD*
1.	IIB		Arrhythmias, Possibly Requiring Drugs And/Or Dc Cardioversion	Moderate	Uncertain	Uncertain	01/07/00	01/07/00	12/10/99	28
2.	III		Arrhythmias, Possibly Requiring Drugs And/Or Dc Cardioversion	Moderate	Not Relat	Possibly	12/10/01	12/10/01	04/05/01	249
3.	III		Arrhythmias, Possibly Requiring Drugs And/Or Dc Cardioversion	Moderate	Not Relat	Possibly	07/19/01	08/22/01	07/19/01	0
4.	III		Arrhythmias, Possibly Requiring Drugs And/Or Dc Cardioversion	Severe	Not Relat	Possibly	11/12/01	11/13/01	07/19/01	116
5.	III		Arrhythmias, Possibly Requiring Drugs And/Or Dc Cardioversion	Moderate	Not Relat	Possibly	04/15/02	.	04/04/02	11
6.	III		Atrial Flutter	Moderate	Not Relat	Possibly	03/11/02	.	02/14/02	25
7.	III		Back Pain	Moderate	Not Relat	Possibly	02/14/02	02/15/02	02/14/02	0
8.	III		Back Pain And Nausea	Mild	Not Relat	Probably	09/17/01	09/17/01	09/17/01	0
9.	III		Bleeding	Mild To Moderate	None	Probable	04/06/01	04/06/01	04/05/01	1
10.	IIB		Bleeding Of Rt Groin	Mild	None	Probable	03/23/00	03/23/00	03/22/00	1
11.	III		Blurred Vision	Mild	Not Relat	Not Relat	11/01/01	11/20/01	05/11/01	174
12.	IIB		Bronchitis/Possible Pneumonia And UTI	Moderate	None	Uncertain	06/27/99	06/29/99	06/09/99	18
13.	IIB		Burn To Chest From Cardioversion	Mild	None	Probable	04/03/00	04/13/00	04/03/00	0
14.	III		Cardiac Perforation And/Or Resulting Hemopericardium And/Or	Severe	Not Relat	Probably	01/10/02	01/14/02	01/10/02	0

Table F-38,* Alphabetical Listing of All Complications Possibly or Probably Related to Procedure or Device (or with "Uncertain" Relationship)

#	Study	Pt ID	AE Symptom	Severity	Rel To Device	Rel To Proc	Date Of Onset	Stop Date	Tx Date	PPD*
			Tamponade							
15.	IIB	606	Chronic Fatigue & Dyspnea	Moderate	None	Uncertain	11/19/99	03/21/00	11/19/99	0
16.	III	1611	Defibrillation Burns	Mild	Not Relat	Probably	12/13/01	12/25/01	12/13/01	0
17.	IIB		Dehydration	Mild	None	Uncertain	04/27/00	04/27/00	04/26/00	1
18.	III		Drug Reactions	Moderate	Uncertain	Uncertain	06/12/01	.	06/08/01	4
19.	III		Femoral Arteriovenous Fistula	Moderate	Not Relat	Probably	04/28/01	05/04/01	04/27/01	1
20.	III		Generalized Discomfort	Moderate	Not Relat	Possibly	07/20/01	07/20/01	07/19/01	1
21.	IIB		Hematoma Right Groin	Mild	None	Probable	10/21/99	01/24/00	10/21/99	0
22.	III		Hosp. For Ablation	Mild	Possibly	Possibly	04/02/02	04/06/02	11/28/01	125
23.	III		Hosp. For Aborted Total AV Node Ablation	Mild	Possibly	Possibly	03/19/02	03/21/02	11/28/01	111
24.	III		Increased Palpitations	Moderate	None	Uncertain	04/09/01	05/02/01	04/05/01	4
25.	III		Increased Weakness And Shaky Sensation W/Mild Nausea, Coldness Of Hands And Nose	Mild To Moderate	None	Uncertain	04/09/01	04/11/01	04/05/01	4
26.	IIB		Infection	Mild	None	Probable	07/09/99	07/11/99	07/08/99	1
27.	III		Infection	Mild To Moderate	None	Probable	04/11/01	04/16/01 - 04/22/01	04/05/01	6
28.	IIB		Left Groin Pain	Mild	None	Probable	11/14/99	12/06/99	11/12/99	2
29.	IIB		Nerve Damage	Mild	None	Probable	04/15/99	07/23/99	04/14/99	1
30.	III		Numbness At Inner Thigh And Incision	Mild	Not Relat	Possibly	07/01/01	07/19/01	04/27/01	65
31.	III		Pauses Asystolic	Severe	Not Relat	Probably	10/25/01	10/31/01	10/24/01	1
32.	III		Pericarditis	Mild	Uncertain	Probable	05/31/01	06/01/01	05/30/01	1
33.	III		Pericarditis	Mild	Possibly	Probably	10/25/01	10/26/01	10/24/01	1
34.	III		Pneumonia	Moderate	Not Relat	Probably	10/25/01	10/28/01	10/24/01	1
35.	III		Posterior Thoracic Skin Burns	Mild	Not Relat	Probably	10/25/01	11/01/01	10/24/01	1

Table F-38,* Alphabetical Listing of All Complications Possibly or Probably Related to Procedure or Device (or with "Uncertain" Relationship)

#	Study	Pt ID	AE Symptom	Severity	Rel To Device	Rel To Proc	Date Of Onset	Stop Date	Tx Date	PPD*
36.	III		Pulmonary Hypertension	Mild	Not Relat	Possibly	07/31/02	.	02/14/02	167
37.	III		Rash From Electrodes	Mild	None	Probable	10/17/00	11/10/00	10/11/00	6
38.	III		Redness On Bilateral Heels And Back Of Head, Blister On Left Index Finger	Mild	None	Probable	10/12/00	10/16/00	10/11/00	1
39.	III		Right Groin Hematoma	Moderate	Not Relat	Possibly	02/19/02	03/08/02	02/14/02	5
40.	III		Rt Groin Ecchymosis	Mild	Not Relat	Possibly	12/04/01	12/18/01	12/03/01	1
41.	III		SA Dysfunction Possibly Requiring A Permanent Pacemaker	Moderate	None	Probable/ None	02/28/01	05/16/01	02/21/01	7
42.	III		SA Dysfunction Possibly Requiring A Permanent Pacemaker	Moderate	Probably	Probably	10/28/01	11/01/01	10/24/01	4
43.	III		Skin Irritation: Erythema To Skin And Itch At Sternum From Cardioversion Pad Site	Moderate	Not Relat	Probably	04/03/02	05/01/02	04/02/02	1
44.	III		Sore Throat	Mild	Not Relat	Probably	12/13/01	12/15/01	12/13/01	0
45.	III		Sore Throat	Mild	Not Relat	Probably	12/17/01	12/18/01	12/17/01	0
46.	III		Sore Throat	Mild	Not Relat	Probably	04/05/02	04/07/02	04/04/02	1
47.	IIB		Sore Throat & Upper Respiratory Infection	Mild	None	Probable	06/12/99	06/14/99	06/09/99	3
48.	III		Sore Throat And Swelling Upper Lip	Mild	Not Relat	Probably	05/31/02	.	05/31/02	0
49.	IIB		Stroke	Moderate	Uncertain	Uncertain	02/04/00	.	02/04/00	0
50.	IIB		Stroke	Mild	None	Uncertain	07/12/00	11/27/00	06/06/00	36
51.	IIB		Superficial Chemical Phlebitis	Mild	None	Uncertain	05/17/99	08/11/99	04/23/99	24
52.	III		SVT	Moderate	None	Uncertain	04/14/01	04/16/01	04/05/01	9

Table F-38,* Alphabetical Listing of All Complications Possibly or Probably Related to Procedure or Device (or with "Uncertain" Relationship)

#	Study	Pt ID	AE Symptom	Severity	Rel To Device	Rel To Proc	Date Of Onset	Stop Date	Tx Date	PPD*
53.	III		Swelling Right Hand	Mild	Not Relat	Possibly	07/20/01	.	07/19/01	1
54.	IIB		Traumatic Injury To Left Leg W/Bleeding Secondary To Coumadin	Moderate	None	Probable	05/25/99	05/16/01	04/27/99	28
55.	IIB		Unable To Take Deep Breath & Right Thigh Numb	Mild	Uncertain	Uncertain	04/15/99	04/29/99	04/14/99	1
56.	III		Weakness - Generalized	Mild	Not Relat	Probably	09/19/01	09/20/01	09/17/01	2
57.	III		Worsened Atrial Fibrillation	Moderate	Not Relat	Possibly	12/12/01	12/13/01	04/05/01	251

*Includes "Major Complications"
**PPD=Post Procedure Day

7.6.9 Comparison of Complications of RFCA

As a context for considering the complications reported for this study, a review of published results for similar procedures was undertaken. While there is ample literature for more established cardiac ablation therapies, including complications, there was sparse evidence in the literature of right atrial ablation for atrial fibrillation.

Table F-39 summarizes four review articles that report complication rates for Accessory Pathway, AV node ablation, AVRNT procedures, and Ventricular Tachycardia for large study populations, generally registry populations. It should be noted that these articles may be reporting complications without regard for the FDA definition of "major complication".

Three publications were identified that report on right atrial RF ablation for AF. Because the nature of complications for cardiac catheterizations is similar, the same format for presenting complications was used to summarize the AF articles, as well. Notably, these article report complications sparsely, if at all, but those complications that are reported are significant in both type and frequency, ranging from 8.3% to 22.2%, involving primarily phrenic nerve injury and sinus node injury.

In comparison to these published complications, the REVELATION® Tx Ablation System procedure has a very strong safety profile of 4.0% over all, with no phrenic nerve injuries and 1.1% sinus node injury, as distinct from underlying or pre-existing sinus node dysfunction.

Table F-39 – Published Complication Rates for Radiofrequency Catheter Ablation (RFCA) in the Right Atrium

Reference	N	Complications (%)													
		Complete AV Block	Valve Damage	Coron. Artery injury/occl	Tamponade	Pericarditis	Pneumothorax	Venous Thrombosis	Pulmonary Emboli	Arterial Thrombosis	CVA/TIA	Bleeding at Puncture	Myocardial Infarction	Other	Death
Accessory Pathway															
Hindricks, et. al. *The Multicentre European Radiofrequency Survey (MERFS): Complications of RFCA of arrhythmias. European Heart Journal. 1993;14**	2222	0.63	0.05	0.0	0.72	NR	NR	0.18	0.09	0.18	0.49	0.32	NR	NR	0.13
Scheinman. *NASPE Survey on Catheter Ablation. Pacing Clin Electrop. 1995;18**	5427	0.17	0.11	0.06	0.13	NR	NR	NF	NF	0.0	0.15	0.06	NR	NR	0.08
Scheinman. *1998 NASPE prospective catheter ablation registry. Pacing Clin Electroph. 2000;23**	654	0.3	0.0	0.16	1.1	NR	NR	0.0	0.16	0.0	0.0	1.99	NR	NR	0.0
Calkins et al. *Catheter ablation of accessory pathways, av nodal reentrant tachycardia, and the av junction. Circulation 1999;99**	500	0.1	NS	0.2	NS	NR	NR	NS	NS	NS	0.2	NS	NR	NR	0.2

* Angkeow P. Calkins H., *Complications Associated with Radiofrequency Catheter Ablation of Cardiac Arrhythmias. Cardiology in Review 2001;9(3):121-130.* A review of 4 major reports, listed separately in this table and a selection of smaller studies specifically for RA RFCA for AF

NR=Not Reported NF=No Frequency Reported but these complications were noted NS=Not specific to the target arrhythmia but was reported for all arrhythmias collectively

123

Table F-39 – Published Complication Rates for Radiofrequency Catheter Ablation (RFCA) in the Right Atrium

Reference	N	Complications (%)													
		Complete AV Block	Valve Damage	Coron. Artery injury/occl	Tamponade	Pericarditis	Pneumothorax	Venous Thrombosis	Pulmonary Emboli	Arterial Thrombosis	CVA/TIA	Bleeding at Puncture	Myocardial Infarction	Other	Death
AVNRT															
Hindricks, et. al. *The Multicentre European Radiofrequency Survey (MERFS): Complications of RFCA of arrhythmias. European Heart Journal. 1993;14**	815	5.07	NR	NR	0.24*	0.24*	0.0	1.11	0.24	NR	0.12	0.24	NR	NR	0.0
Scheinman. *NASPE Survey on Catheter Ablation. Pacing Clin Electrop. 1995;18**	5423	0.11	NR	NR	0.33*	0.33*	0.09	0.09	0.0	NR	0.00	0.06	NR	NR	0.0
Scheinman. *1998 NASPE prospective catheter ablation registry. Pacing Clin Electroph. 2000;23**	1197	0.74	NR	NR	0.0	0.0	0.08	0.08	0.08	NR	0.0	0.49	NR	NR	0.0
Calkins et al. *Catheter ablation of accessory pathways, av nodal reentrant tachycardia, and the av junction. Circulation 1999;29**	373	1.3	NR	NR	NS	NS	NS	NS	NS	NR	NS	NS	NR	NR	0.0

* Angkeow P. Calkins H., *Complications Associated with Radiofrequency Catheter Ablation of Cardiac Arrhythmias. Cardiology in Review 2001;9(3):121-130.* A review of 4 major reports, listed separately in this table and a selection of smaller studies specifically for RA RFCA for AF

NR=Not Reported NF=No Frequency Reported but these complications were noted NS=Not specific to the target arrhythmia but was reported for all arrhythmias collectively *=Reported as a combined complication (tamponade/pericarditis)

124

Table F-39 – Published Complication Rates for Radiofrequency Catheter Ablation (RFCA) in the Right Atrium

Reference	N	Complications (%)													
		Complete AV Block	Valve Damage	Coron. Artery injury/occl	Tamponade	Pericarditis	Pneumothorax	Venous Thrombosis	Pulmonary Emboli	Arterial Thrombosis	CVA/TIA	Bleeding at Puncture	Myocardial Infarction	Other	Death
AV Junction															
Hindricks, et. al. *The Multicentre European Radiofrequency Survey (MERFS): Complications of RFCA of arrhythmias. European Heart Journal. 1993;148*	900	NR	0.11[f]	NR	NR	NR	NR	1.00	0.22	NR	0.0	0.0	0.0	NR	0.11
Scheinman. *NASPE Survey on Catheter Ablation. Pacing Clin Electrop. 1995;18**	2084	NR	0.0[f]	NR	NR	NR	NR	0.0	0.0	NR	0.1	0.0	0.05	NR	0.2
Scheinman. *1998 NASPE prospective catheter ablation registry. Pacing Clin Electroph. 2000;23**	646	NR	0.15[f]	NR	NR	NR	NR	0.0	0.0	NR	0.0	0.30	0.0	NR	0.15
Calkins et al. *Catheter ablation of accessory pathways, av nodal reentrant tachycardia, and the av junction. Circulation 1999;29**	121	NR	NS	NR	NR	NR	NR	NS	0.82	NR	0.82	NS	0.0	NR	0.65

* Angkeow P. Calkins H., *Complications Associated with Radiofrequency Catheter Ablation of Cardiac Arrhythmias. Cardiology in Review 2001;9(3):121-130.* A review of 4 major reports, listed separately in this table and a selection of smaller studies specifically for RA RFCA for AF

NR=Not Reported NF=No Frequency Reported but these complications were noted NS=Not specific to the target arrhythmia but was reported for all arrhythmias collectively [f]=Reported here as Significant Tricuspid Regurgitation

125

Table F-39 – Published Complication Rates for Radiofrequency Catheter Ablation (RFCA) in the Right Atrium

Reference	N	Complications (%)													
		Complete AV Block	Valve Damage	Coron. Artery injury/occl	Tamponade	Pericarditis	Pneumothorax	Venous Thrombosis	Pulmonary Emboli	Arterial Thrombosis	CVA/TIA	Bleeding at Puncture	Myocardial Infarction	Other	Death
Ventricular Tachycardia															
Hindricks, et. al. *The Multicentre European Radiofrequency Survey (MERFS): Complications of RFCA of arrhythmias. European Heart Journal. 1993;14**	320	0.31	NR	NR	0.63	NR	NR	NR	0.63	1.0	1.26	0.63	NR	0.63§	0.31
Scheinman. *NASPE Survey on Catheter Ablation. Pacing Clin Electrop. 1995;18**	844	0.12	NR	NR	0.71	NR	NR	NR	NR	0.12	NR	NR	NR	0.36	0.0
Scheinman. *1998 NASPE prospective catheter ablation registry. Pacing Clin Electroph. 2000;23**	201	NR	NR	NR	1.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	1.5
Calkins et al. *Catheter ablation of accessory pathways, av nodal reentrant tachycardia, and the av junction. Circulation 1999;29**	146	1.4	0.7	NR	2.7	NR	NR	NR	NR	NR	1.26	0.7	NR	NR	2.7

* Angkeow P. Calkins H., *Complications Associated with Radiofrequency Catheter Ablation of Cardiac Arrhythmias. Cardiology in Review 2001;9(3):121-130.* A review of 4 major reports, listed separately in this table and a selection of smaller studies specifically for RA RFCA for AF

NR=Not Reported § Peripheral embolism

126

Table F-39 – Published Complication Rates for Radiofrequency Catheter Ablation (RFCA) in the Right Atrium

Reference	N	Complications (%)													
		Complete AV Block	Valve Damage	Coron. Artery injury/occl	Tamponade	Pericarditis	Pneumothorax	Venous Thrombosis	Pulmonary Emboli	Arterial Thrombosis	CVA/TIA	Bleeding at Puncture	Myocardial Infarction	Other	Death
Atrial Fibrillation (treated with linear lesions for RA compartmentalization or a RA 'MAZE' procedure)															
Gaita et al., *Atrial mapping and radiofrequency catheter ablation in patients with idiopathic atrial fibrillation. Circulation 1998;97*	16	No complications reported													
Natale et al., *Catheter ablation approach on the right side only for paroxysmal AF. PACE 2000;23.*	18	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	§16.6 ¥ 22.2	NR
Garg, et al., *Right Atrial Compartmentalization Using Radiofrequency Catheter Ablation of Management of Patients with Refractory AF. J Cardiovasc Electrophysiol, 1999;10*	12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	§8.3	0.0

NR=Not Reported

NF=No Frequency Reported but these complications were noted

NS=Not specific to the target arrhythmia but was reported for all arrhythmias collectively

§ = SA dysfunction
¥ = Phrenic Nerve Injury

127

Table F-40 – Cardima Complications (Device Or Procedure Related)

Reference	N	Complications (%)**													
		Complete AV Block	Valve Damage	Coron. Artery injury/occl	Tamponade	Pericarditis	Pneumothorax	Venous Thrombosis*	Pulmonary Emboli	Arterial Thrombosis	CVA/TIA	Bleeding at Puncture	Myocardial Infarction	SA Node Dysfunction	Death
RFCA for Paroxysmal Atrial Fibrillation															
REVELATION Ablation System Study	99	0.0	0.0	0.0	0.01	0.02	0.0	0.01	0.0	0.0	0.02	0.01	0.0	0.01	0.0

* DVT

** AV Fistula=0.01%, not reported for any other procedure.

128

7.6.10 Catheter Performance

Catheter performance was evaluated on five fundamental characteristics, as illustrated in Table F-41. Overall catheter performance was rated "Very Good" to "Excellent" 78.5% of the time. All five of the fundamental characteristics were rated "Very Good" to "Excellent" in more than 55% of the ratings, with the most ratings (83.6%) for "Very Good" to "Excellent" ratings for "RF Energy Application" of the REVELATION® Tx.

Table F-41 - Investigator's Performance Evaluation of the REVELATION® Tx Microcatheter (n=98 [a])

Characteristics	Rating (%)				
	Excellent	Very Good	Avg.	Fair	Poor
Ease of Catheter Placement	36.7	37.8	20.4	5.1	0.0
Stability of Catheter Placement	42.9	34.7	17.4	4.1	1.0
Radiopacity of Catheter after Placement	49.0	32.7	14.3	4.1	1.0
Pacing	28.6	27.6	25.5	3.1	15.2
RF Energy Application	41.8	41.8	11.2	5.1	0.0
Overall System Performance	31.6	46.9	18.4	3.1	0.0

[a] Except for pacing, where n=79. Pacing was not always evaluated.

The relatively weakest performance indicator was for pacing, with 56.2% of the ratings being "Very Good" to "Excellent"; 25.5% rated the performance as "Average".

The NavAblator™ 4 mm "hot tip" ablation catheter was also evaluated using a similar slate of characteristics. The NavAblator™ was introduced into clinical use for the first time during this study and its performance ratings reflect its level of maturity in contrast to the REVELATION® Tx.

Table F-42 reports the evaluation results of the NavAblator™.

Table F-42- Investigator's Performance Evaluation of the NavAblator™ (n=48[a])

Characteristics (n=48)	Rating (%)				
	Excellent	Very Good	Average	Fair	Poor
Ease of NavAblator™ Placement	29.2	10.4	20.8	25.0	14.6
Ease of Deflection	31.3	12.5	14.6	25.0	16.7
Stability of Placement	31.3	16.7	31.3	12.5	8.3
Stability of Deflectable tip	31.9	19.2	31.9	4.3	12.8
Radiopacity	51.1	27.7	21.3	0.0	0.0
Pacing	44.4	16.7	38.9	0.0	0.0
RF Energy Application	41.3	19.6	26.1	13.0	0.0
Overall NavAblator™ Performance	34.0	6.4	14.9	36.7	8.5

[a] Indicates the range of sample sizes for the individual characteristics rated.

The overall performance of the NavAblator™ was rated as "Average" and above by 55.3% of the users, with 40.4% of them rating it "Very Good" to "Excellent". Pacing and RF Energy Application each were rated as "Very Good" to "Excellent" by more than half the users (61.1% and 60.8%, respectively).

The relatively lower ratings for the NavAblator™ are believed to be largely due to a sub-optimal deflection mechanism that has been improved during the course of the investigation.

7.6.11 Customer Experience Reports of Device Performance

Customer reports about the performance of the REVELATION® Ablation System and any of its devices or components were recorded.

The nature of the reports suggests a typical design evolution in which earlier products may show some room for process improvements and, once addressed, those complaints diminish.

At the beginning of the study there were some complaints recorded concerning some electrodes or thermocouples on a given catheter failing to perform. The volume of those complaints was substantially reduced by the time of this report.

Likewise, no further reports of lamination failures have been documented since the process improvement was implemented.

Occasional electrode failures on a device of this complexity are not believed to be unexpected or unusual.

Table F-43, Customer Experience Reports - REVELATION® Tx Catheters

ID	Failure Mode	Impact on Patient	Site	Date of Event	Failure Investigation Results
1999000	REVELATION Tx stuck in the Naviport. We could not remove the catheter from the NAVIPORT®. The entire assembly was removed without patient incident.	No Impact	JOHNS HOPKINS Hospital	3/31/1999	THV lamination lifted up from the shaft surface in some areas and build up of coagulum decreased clearance in NAVIPORT lumen when deflected. Corrective action included development of technical guidance on "ramped" RF energy delivery to prevent occurrence of coagulum. THV lamination process improved to include "reflow" to assure THV laminate flows into shaft.
1999000	Coagulum formed on electrodes. Return for evaluation, approximately 50 deliveries of RF energy through the catheter before the coagulum formation.	No Impact	JOHNS HOPKINS Hospital	3/31/1999	Technical guidance on "ramped" RF energy delivery to prevent occurrence of coagulum was distributed.
1999000	REVELATION Tx was a tight fit in the NAVIPORT - it did not slide out easily after the ablation procedure and some coagulum had formed on the REVELATION Tx.	No Impact	Fairfax Hospital	3/19/1999	THV lamination lifted up from the shaft surface in some areas and build up of coagulum decreased clearance in NAVIPORT lumen when deflected. Corrective action included development of technical guidance on "ramped" RF energy delivery to prevent occurrence of coagulum. THV lamination process improved to include "reflow" to assure THV laminate flows into shaft.
1999000	Rough burrs were felt on proximal electrode 8 and 5 after completing one linear radiofrequency ablation and removing the Revelation Tx for cleaning.	No Impact	Lancaster General Hospital	4/14/1999	THV lamination lifted up from the shaft surface in some areas. Electrode coils stretched at the proximal edge of electrodes. THV lamination process improved to include "reflow" to assure THV laminate flows into shaft. Tighter pitch of coil winding reduced stretching in future lots.

132

Table F-43, Customer Experience Reports - REVELATION® Tx Catheters

ID	Failure Mode	Impact on Patient	Site	Date of Event	Failure Investigation Results
1999000	First device (P0757) did not record from electrodes 1 and 2 on electrogram. Second device (P0909) stopped recording from electrodes 5 and 6 after ablation. Third device (P0700) returned due to "roughness" of THV over electrode	No Impact	Lankenau Hospital	4/23/1999	Investigation found the first device with proximal connector opened and insulation cut. There was detachment of copper wires in two of the three returned REVELATION devices. However, the catheters appear to have been tampered with, so it was difficult to determine if the catheter was damaged during the procedure, or by the user before or after the procedure. In addition, roughness of THV at the electrodes were observed. This is probably due to retraction out of the Naviport and related to the lack of reflow in the lamination process.
1999000	Thermocouples on electrode 8 never registered temperature, therefore never delivered radio frequency energy.	No Impact	Fairfax Hospital	4/27/1999	TC8 / E8 were found to be functional. Therefore, the discrepancy reported by the complainant could not be verified.
1999000	Display on monitor read "temperature at boiling point" but temperature was okay. Coagulum was discovered on the device.	No Impact	University of Chicago	6/3/1999	During procedure adapter cable was changed out and device performed as expected. Electrical testing demonstrated that device is functional. Adapter cable was at fault. No further action taken.
1999000	High impedance shutoff during ablation on several occasions. Entire system to be returned. Clinical Research Assistant believes it was the generator, but is returning entire system for more thorough evaluation.	No Impact	Massachusetts General Hospital	8/18/1999	High impedance shutoff was likely due to wire failures at TC1, E7 and E8. Wire failures may be due to corrosion from incomplete cleaning process following soldering. Cleaning process improved to assure thorough cleaning.

133

Table F-43, Customer Experience Reports - REVELATION® Tx Catheters

ID	Failure Mode	Impact on Patient	Site	Date of Event	Failure Investigation Results
1999000	Catheter or cable was making buzzing / crackling sounds.	No Impact	Lancaster General Hospital	10/21/1999	Could not recreate a buzzing or crackling noise, when the REVELATION Tx device was tested together with the returned cable during a system check. The device was electrically functional according to the Cirris testor. In addition, no cosmetic damage was observed.
1999000	No temperature reading electrodes 1,2 and 4.	No Impact	Lankenau Hospital	11/19/1999	Copper wires found detached on all TCs and electrodes. Wire failures may be due to corrosion from incomplete cleaning process following soldering. Cleaning process improved to assure thorough cleaning.
2001000	Lead 2 would not allow us to ablate.	No Impact	Wisconsin Center for Clinical Research	4/5/2001	Continue to monitor failure mode, as incident rate is low.
	E2 did not function during a portion of the procedure (IVC-SVC lesion).	No Impact	Wisconsin Center for Clinical Research	4/5/2001	Could not confirm failure.
	Noisy ECG Signal	No Impact	Wisconsin Center for Clinical Research	4/5/2001	Was intermittent. Could not confirm in the mfgr lab. Continue to monitor failure mode, as incident rate is low.

124

Table F-43, Customer Experience Reports - REVELATION® Tx Catheters

ID	Failure Mode	Impact on Patient	Site	Date of Event	Failure Investigation Results
2001000	Leads 3-8 could not conduct ECG signals. Tracings were very noisy or missing. This occurred after the catheter was removed to check for coagulation, cleaned and reinserted.	No Impact	Wisconsin Center for Clinical Research	5/17/2001	Investigation found open circuits on E4 and E5. Cause undetermined. Continue to monitor failure mode, as incident rate is low.
2001000	Catheter failed to provide accurate temperature. Readings went down to low temperature cutoff, but not up.	No Impact	Inova Fairfax Hospital	6/8/2001	Investigation found open circuits on E2 and E6. Cause undetermined. Continue to monitor failure mode, as incident rate is low..
2001000	Thermocouple failures on electrodes 1 thru 3 after the first series of 8 ablations. The Tx was replaced and the ablation continued without further failures.	No Impact	Carle Heart Center	10/17/2001	It was noted that the Heparin drip was not flowing enough. The Tx & NAVIPORT were removed and some mild coagulum was noted on electrode 1. The Tx was cleaned and reinserted through the Naviport and a continuation of the first line was started. The RF Generator display started to show high temp reading (50 degrees C) and then would cut out with LL, the low temp error message. This happened three times on the first three electrodes Investigation of failed device showed that it met all electrical specifications.
2002000	The EP lab manager reported that the catheter had some problems at first until changing to a second catheter cable. It was not sure if it was a problem w/the catheter or the cable.	No Impact	Carle Heart Center	1/8/2002	None taken since complaint could not be confirmed and device met electrical test requirements.
2002000	Thermocouple #1 did not work properly when ablation was attempted	No Impact	Sequoia Hospital	4/2/2002	Could not reproduce failure. Device met specifications. No corrective action is being taken since the.

135

Table F-43, Customer Experience Reports - Cables

ID	Failure Mode	Impact on Patient	Location/ Site	Date of Event	Corrective Action/Mitigation
2001000	Tear in package. When shipment was received, product was open, sterile barrier was broken.	No Impact	Wisconsin Center for Clinical Research	5/7/2001	The cable was returned with the sterile barrier compromised.
2002000	Per RGA 10644, the catheter had some problems at first until changing to a second catheter cable. It was not clear if it was the problem with the connector or the connection. Cables used are being returned under RGA 10643.	No Impact	Carle Heart Center	1/8/2002	Part of # 2002000240, above. Cable was inspected and passed all testing. No corrective action will be taken since the device met specifications and the complaint rate for this problem is so low. This failure mode will continue to be monitored to determine if future corrective action is warranted.
2002000	Per RGA 10644, the catheter had some problems at first until changing to a second catheter cable. It was not sure if it was the problem with the connector or the connection. Cables used are being returned under RGA 10643.	No Impact	Carle Heart Center	01/08/02	This is same as above, second cable involved. Could not confirm failure and device met specification during analysis testing.

Table F-43, Customer Experience Reports - Cables

ID	Failure Mode	Impact on Patient	Location/ Site	Date of Event	Corrective Action/Mitigation
2002000	ECG cable did not give good signals when connected. It was replaced with a second cable that worked fine.	No Impact	Sequoia Hospital	4/2/2002	Analysis confirmed loose connection at the yoke or pin of the #2 wire. Complaint data were reviewed for 01/1997 to present and there were no other complaints for ECG cables. Due to the low failure rate, no corrective action is being taken at this time. This failure mode will continue to be monitored to determine if future corrective action is warranted.

157

Table F-43, Customer Experience Reports - Tx Select™ Switchbox

ID	Failure Mode	Impact on Patient	Location/ Site	Date of Event	Corrective Action/Mitigation
2001000	Connector marked "RF Generator" on switchbox has missing screw	No Impact	Clinical Inventory	12/10/01	No corrective action was taken due to the low complaint failure rate
2002000	During an ablation procedure the IBI RF Generator repeatedly shut down.	No Impact	General Hospital Center at Passaic	03/15/02	The device met specifications. The failure is a default "feature" of the IBI generator that occurs when switching from one electrode pair to the next with the Tx Select Switchbox too slowly. The physician was retrained on the use of the Tx Select Switchbox and the IBI Generator during the procedure. Corrective action was not deemed necessary at this time.
2002000	No temp reading on the RF Generator with the switchbox on position 1. The Tx catheter was exchanged and again there was no temp reading on position 1. All other switch positions gave temp readings.	No Impact	Brotman Medical Center	06/27/02	The need for corrective action will be determined at the conclusion of the investigation.

138

Table F-43, Customer Experience Reports - NavAblator

ID	Failure Mode	Impact on Patient	Location/ Site	Date of Event	Corrective Action/Mitigation
2001000	Handle did not deflect tip. The NavAblator, when tested outside of the patient, would not deflect more than 90 degrees.	No Impact	Lankenau Hospital	5/30/2001	Investigation found set screw for pull wire assembly set short, not permitting full deflection. The manufacturing processes were reviewed with all employees who assemble the NavAblator.
2002000	Handle did not deflect tip. NavAblator would not fully deflect.	No Impact	Inova Fairfax Hospital	6/8/2001	Investigation found set screw for pull wire assembly set short, not permitting full deflection. The manufacturing processes were reviewed with all employees who assemble the NavAblator.
2002000	NavAblator has adhesive on shaft in the area over the product.	No Impact	n/a	10/31/2001	Packaging included adhesive strip over top of tray to prevent device from coming out of tray. In some cases residue from this adhesive strip adhered to surface of shaft. No customer field reports have been received on this but a Cardima rep noticed it on a few occasions. A new tray that mitigates the need for such a retaining device has been developed for the NavAblators and NAVIPORTS (9F and 10F)

129

7.7 Criteria for Measuring Safety and Effectiveness

7.7.1 Clinical Endpoints

- The primary clinical endpoints for this study are:
  - Frequency of any spontaneous symptomatic episodes of AF experienced by the subjects.
  - Incidence of adverse effects

As shown in Section 7.6.3, pages 77 through 84, and in Tables F28a through F-29b, the results indicate significant reduction in the frequency of spontaneous symptomatic AF episodes experienced by the patients in this study, with an average reduction of 73.6% ± 5.2% and a median reduction of 93.8% at six months.

The incidence of adverse effects is less than or comparable to those reported in the literature for other RFCA in the right atrium and for ventricular RFCA, as well, and far below those reported for the few published studies of RFCA for AF in the right atrium.

In addition, according to the "definition of clinical success" the confidence intervals for the results at three and six months demonstrate an unequivocal success (see Section 7.6.3, page 77).

- The secondary clinical endpoint is:
  - Quality of Life based upon changes in the scores of the SF-36 and AFSS questionnaires

As shown in Section 7.6.6, pages 88 through 91, these subjects demonstrated improvement in all eight SF-36 quality of life scales at both the three and six month follow-up assessments. There were quite substantial and clinically significant and highly statistically significant improvements for four of the eight domains (Role Physical, Role Emotional, Vitality, and Social Functioning) at both of these follow up assessments, clearly indicating overall substantial patient benefit.

7.7.2 Procedural Endpoints

The procedural effectiveness is demonstrated by the presence at the line(s) of ablation of either split potentials or a reduction in electrogram amplitudes from pre-ablation to post-ablation.

The data reported in Section 7.5.3, pages 72 through 74, are not sufficient to demonstrate either success or failure for the procedure, although the chronic results strongly suggest that the acute results were successful.

7.8 Rationale for Combining Phase IIb and Phase III

The protocols for Phase IIb and in Phase III of this study shared significant similarities. The similarities and differences of the protocols are summarized in Table F-45.

The initial feasibility protocol (Phase IIa, Original IDE#G970280, in a letter from FDA dated December 19, 1997) was approved to study feasibility and safety. However, effectiveness was also assessed by the extent of symptomatic episode reduction at six months based upon event monitor recordings transmitted during the follow up period. Safety would be assessed based upon the incidence of complications.

December, 12, 1998 (Supplement #13) an "expanded feasibility", Phase IIb, was approved with similar objectives and endpoints as Phase IIa, but with more specific assessment criteria.

In June, 2000, (Supplement #26) Phase III of this study was approved. The study objectives and follow up durations and assessment measures for Phase IIb and Phase III are identical. The patient selection criteria are similar except that Phase III extended the upper age limit to 80 from 75 years and permitted a prior CVA if ≥6 mo past as opposed to excluding any prior CVA. The increased age limit would not introduce a positive bias into the study, nor would the addition of patients with a prior CVA, but it did expand the study population.

These slight patient selection differences do not affect pooling the data from these two phases of the study, consistent with the encouragement issued by FDA to maintain the protocol for Phase III as closely as possible to Phase II to facilitate pooling the data from the two phases.

Table F-45 summarizes the study phases and their similarities. The study phases are presented in this table from most recent to least recent.

Table F-44 - Summary of Study Phases and Key Features of Each

Study Phase	# Sites	N	Study Objective(s)	Selection Criteria	Study Population	Study Duration	Study Endpoints
III	20	61	Demonstrate the safety and effectiveness of the REVELATION® Tx to map, pace and create linear lesions in the right atrium of patients with drug refractory symptomatic paroxysmal atrial fibrillation. Dr. may use the Cardima **NavAblator™** or "standard institutional procedure" (hot tip catheters) to complete the isthmus, if necessary.	Drug refractory (2 AADs) PAF with >2 symptomatic episodes/30 day period; ≥21 yrs, ≤**80** yrs; absence of structural heart disease.	Paroxysmal Atrial Fibrillation with failed drug therapy.	24 months (with 6 month episode reduction data and safety data from 6, 12, and 24 months)	Reduction in Symptomatic AF Episode Frequency from Baseline to 6 months of 50% or greater (with 50% or greater number of subjects reporting 50% or greater reduction); Incidence of major complications; Improved Quality of Life as measured by two established assessment devices, the SF-36 and the AFSS.
IIb	10*	38	Demonstrate the safety and effectiveness of the REVELATION® Tx to map, pace and create linear lesions in the right atrium of patients with drug refractory symptomatic paroxysmal atrial fibrillation. Dr. may use "standard institutional procedure" (hot tip catheters) to complete the isthmus, if necessary.	Drug refractory (2 AADs) PAF with >2 symptomatic episodes/30 day period; ≥21 yrs, ≤**75** yrs; absence of structural heart disease.	Paroxysmal Atrial Fibrillation with failed drug therapy.	24 months (with 6 month episode reduction data and safety data from 6, 12, and 24 months)	Reduction in Symptomatic AF Episode Frequency from Baseline to 6 months of 50% or greater (with 50% or greater number of subjects reporting 50% or greater reduction); Incidence of major complications; Improved Quality of Life as measured by two established assessment devices, the SF-36 and the AFSS.

143

Table F-44 - Summary of Study Phases and Key Features of Each

Study Phase	# Sites	N	Study Objective(s)	Selection Criteria	Study Population	Study Duration	Study Endpoints
I (IIa)	3	10	Demonstrate the feasibility of using this catheter to safely treat atrial fibrillation (AF) by creating linear lesions in the right atrium. In the event that the use of the Cardima device is unsuccessful, other treatment alternatives may be employed to treat the patient as deem clinically appropriate.	Drug refractory (2 AADs) PAF, >1 symptomatic episode per month; **≥21, ≤75** yrs	Paroxysmal Atrial Fibrillation with failed drug therapy	6 months	To evaluate whether the REVELATION Tx ("Pathfinder AFTC") can be safely used to create linear lesions in the right atrium to treat atrial fibrillation. Secondary endpoints included whether patients report an absence or reduction in frequency and/or duration of any spontaneous episodes of AF. Incidence of complications associated with lesion placement in RA.

*Phase IIb was approved with 10 sites, later, "expanded" to 15.

144

7.8.1 Lesion Sets and Ablation Catheters

"The optimal" lesion set is not identified by this study, nor was it an explicit objective of the protocol. This study was only intended to identify and suggest likely trajectories for consideration.

Correspondence (e-mail) dated November 16, 1998, between the Sponsor and the Agency reported that it was understood [by FDA] that a specific lesion set for the protocol could only be a guide and that some "...deviations may occur based on best medical judgment...." and that "[Such] deviations presumably will not disqualify patients from data analysis.

It should be noted that the "optimal" lesion set for the catheter-based RF ablation "maze" procedure has not been identified according to current literature, as indicated by the continuing controversy over whether right atrial lesions or left atrial lesions are more effective in treating AF. The mechanism of atrial fibrillation is still not fully understood, but is generally believed to be the result of multiple-reentrant wavelets occurring randomly in the atrium. Changes in the myocardium that often occur with aging facilitate development of a substrate to support such reentrant wavelets. The creation of linear barriers (lesions) in the atrial wall has been shown to block these wavelets. However, no specific lesion pattern has been shown to be more effective than another in creating these barriers.

Dr. Abraham Kocheril has reported on 29 drug refractory PAF patients prospectively studied with the REVELATION® (no thermocouples) with the Cardima NAVIPORT® to create a variety of lesions, always including an isthmus line[10]. In his study, lesions are created during sustained AF. This study further indicates that no precise combination of lesions, approaches for the RFCA treatment of AF has yet been defined.

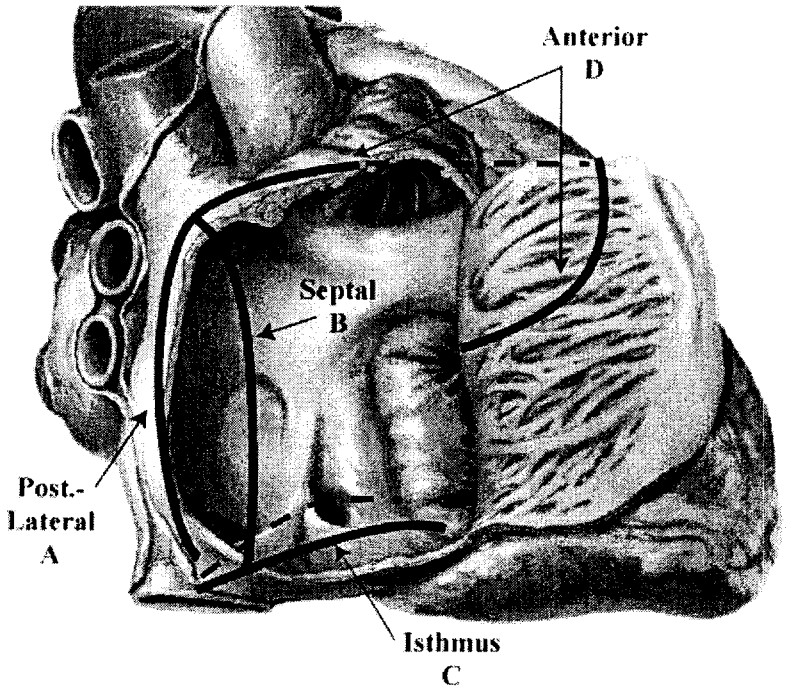
In a prospective study of 18 patients with drug refractory paroxysmal AF, Dr. Andrea Natale used variations of three (3) different right atrial lesion patterns (all of which included some variation of an isthmus line) and found no differences in outcomes relative to lesion pattern, indicating that lesion patterns may be best

determined by the mapping procedure or physician's judgment (e.g., when arrhythmia prevents mapping/pacing; prior ablation at that site; no medical indication for that trajectory)[11].

Dr. Hein Wellens reports that it has been shown "...that a large reentrant wave in the right atrium may become unstable, giving rise to secondary smaller wavelets resulting in AF." Dr. Wellens further reports, that catheter ablation of the right atrial isthmus resulted in the prevention of AF in combination with pharmacological therapy[12]. However, isthmus ablation alone has not proven to be effective for AF.

All three phases of the investigation of the Cardima REVELATION® Tx Ablation System suggested, but did not require, a lesion set that included a line at the isthmus. Figure F-10 illustrates the approximate location of the four possible lesion locations discussed in the protocol(s) under which this study was conducted.

Figure F-10, Lesion Trajectories



As shown in Figure F-7, the suggested lesion sets in this study include lateral, septal, and isthmus lines and, at the investigator's discretion, sometimes an anterior line. Table F-45 summarizes the lesion sets actually created in the patients included in this report.

Table F-45 Lesion Lines Ablated during RF ablation treatment

Lesion Lines	Frequency	%
ABC	78	82.1
AB (no isthmus)	6	6.3
ACD	5	5.2
AC	2	2.1
ABCD	2	2.1
BC	1	1.1
BCD	1	1.1
Total	95	100.0

A = posterolateral, B = posteroseptal, C = isthmus, D = anterior

In over 90% of the subjects (86/95, 90.5%), at least three of the four possible lines of ablation were ablated. Six subjects did not have the isthmus line ablated and had only the posterolateral and posteroseptal lines treated (AB). The majority of the subjects (78/95, 82.1%) were treated with the posterolateral, posteroseptal, and isthmus lines (ABC).

It is important to note that all three phases of the study permitted the use of "standard institutional procedure" to complete the isthmus line, if necessary.

The anatomy of the isthmus includes varying ridges and valleys where the atrial wall can vary in thickness from 2-3mm to 2-2.5cm in thickness. This challenging anatomy may sometimes require a conventional "hot tip" ablation catheter to achieve sufficient tissue contact for optimal lesion creation rather than the flexible, linear arrayed REVELATION Tx. The conventional "hot tip" ablation catheter is typically a 7Fr or 8Fr 4mm tip ablation catheter with a single ablation electrode and two to three mapping and/or pacing electrodes.

Each phase of the study permitted participating investigators to use the standard "hot tip" ablation catheter stocked by their institution when the REVELATION® Tx was not effective in the isthmus region.

Prior to the approval of the Phase III protocol, FDA advised Cardima that it would be necessary to specify one RF ablation catheter as the option for the isthmus line when the REVELATION® Tx could not achieve the desired lesion depth in that region. Because there were no other catheters approved for treating AF, Cardima elected to introduce its own 4mm "hot tip" electrode RF ablation catheter, called the NavAblator™ as an additional investigational device for creating lesions at the isthmus.

Thus, Phase III was approved to include the NavAblator™, a 4mm "hot tip" ablation catheter that "...is specifically intended as an *optional* device for ablation at the ""cardiac isthmus"" (page 16 of the protocol). However, the protocol still permitted the use of "standard institutional procedure", just as both prior phases had done.

The introduction of the Cardima 4mm "hot tip" ablation catheter, the NavAblator™, made the Cardima REVELATION® Tx Ablation System self-contained, so that the labeling for the Cardima system would not require the creation of the isthmus (flutter) line with a non-system catheter.

In all cases, the REVELATION® Tx Microcatheter was used to complete the lateral, septal, or anterior lines. In some cases, it was also used to complete the isthmus line, as well.

It is important to note that the "optional" use of non-study 4mm "hot tip" ablation catheters for the isthmus line occurred randomly across all phases of the study. When the REVELATION® Tx Microcatheter could not achieve bi-directional block at the isthmus, a conventional "hot tip" RF ablation catheter was used. The "hot tip" ablation catheter was a tip electrode, 6 Fr to 8 Fr RF ablation catheter, whether it was Cardima's catheter or the "standard institutional procedure". And, in all cases, the "hot tip" catheter was only used to complete the flutter line.

Table F-46 identifies the catheters used to create the isthmus line in this study.

Table F-46, Catheters Used To Ablate The Isthmus Line

Catheters	Frequency/n	%
NavAblator Only	34/89[a]	38.2
REVELATION Tx only	20/89	22.5
Other only	18/89	20.2
REVELATION Tx, Other	10/89	11.2
Isthmus line not ablated	6/89	6.7
NavAblator, Other	5/89	5.6
REVELATION Tx, NavAblator	2/89	2.2
Isthmus Line Not Ablated	6	
Total	95	100.0

[a] NavAblator used for Isthmus only, Tx used for lateral and septal lines, plus isthmus and anterior lesions.

As illustrated in Table F-46, non-study catheters were used exclusively to ablate the isthmus line in 18/89 (20.2%) subjects who received an isthmus line ablation. The NavAblator™ was employed exclusively in 34 subjects (35.8%), in combination with other catheters in five subjects, and with the REVELATION® Tx in two subjects. The REVELATION® Tx was employed exclusively in 20 subjects (21.1%) and with other catheters in 10 subjects (10.5%)

The "hot tip" catheters used in this study to create the isthmus line are identified in Table F-47 with the key features to illustrate their similarities. Fully half of the non-study catheters used to create isthmus lines were the EPT Blazer (16/32, 50%). Slightly more than twenty percent (7/32, 21.9%) were created with the Navistar and the balance was Medronic and Chili CoolTip.

Table F-47, Hot-Tip Catheters in REVELATION Tx Study

Device Name	# Used
Blazer	16
Navistar	7
Medtronic	6
Chili/CoolTip	3

Table F-48, Listing of Other "Hot Tip" Catheters Used for Isthmus Lesions

Device Name	Manufacturer	PMA #	Approval Date	Indications	French Size	Tip
Blazer II HTD Temperature Ablation Catheters	EP Tech (BSCI)	P920047	10/28/94	1. Interruption of accessory atrioventricular conduction pathways associated with tachycardia; 2. For treatment of AV nodal re-entrant tachycardia; 3. Creation of complete AV nodal block in patients with rapid ventricular response to an atrial arrhythmia - typically chronic, drug refractory atrial fibrillation	7F; 8F	4 mm tip (7F); 5 mm tip (8F); Quadripolar
Cordis Webster Celsius Diagnostic/Ablation Deflectable Tip Catheter	Cordis Webster	P950005	09/30/97	1. Cardiac electrophysiological mapping 2. Interruption of accessory atrioventricular (AV) conduction pathways associated with tachycardia; 3. The treatment of AV nodal re-entrant tachycardia 4. Creation of complete AV nodal block in patients with a difficult to control ventricular response to an atrial arrhythmia	6F; 7F	4 mm tip electrode
NAVI-STAR Diagnostic/Ablation Catheter	Cordis Webster (BioSense Webster)	P990025	06/15/00	1. Catheter-based atrial and ventricular cardiac mapping 2. Interruption of accessory atrioventricular (AV) conduction pathways associated with tachycardia; including persistent junctional re-entrant tachycardia (PJRT) and Mahaim fibers 3. The treatment of AV nodal re-entrant tachycardia 4. Creation of complete AV nodal block in patients with a difficult to control ventricular response to an atrial arrhythmia 5) location information (when used with the CARTO EP Navigation System)	7F	4 mm tip electrode

Table F-48, Listing of Other "Hot Tip" Catheters Used for Isthmus Lesions

Device Name	Manufacturer	PMA #	Approval Date	Indications	French Size	Tip
Chilli Cooled Ablation System	Cardiac Pathways (BSCI)	P980003	02/02/99	1. Cardiac electrophysiological mapping 2. Delivering diagnostic pacing stimuli 3. Radiofrequency ablation of mappable ventricular tachycardias attributable to ischemic heart disease or cardiomyopathy in patients who have failed drug therapy	NR	4 mm tip electrode
Chilli Cooled Ablation System (with Tracking)	Cardiac Pathways (EP Tech./BSCI)	P990054	03/17/00	1. Cardiac electrophysiological mapping 2. Delivering diagnostic pacing stimuli 3. Radiofrequency ablation of mappable ventricular tachycardias attributable to ischemic heart disease or cardiomyopathy in patients who have failed drug therapy 4. Provide catheter location information (when used with the Arrhythmia Mapping and Tracking System)	7F	4 mm tip electrode
Atakr RF Ablatr	Medtronic CardioRhythm	P930029	02/09/95	1. Interruption of accessory atrioventricular (AV) conduction pathways associated with tachycardia; 2. For the treatment of AV nodal re-entrant tachycardia 3. Creation of complete AV nodal block in patients with a difficult to control ventricular response to an atrial arrhythmia 4. Endocardial recording or stimulation	NR	4 mm tip electrode
RF Marinr	Medtronic CardioRhythm	P930029	02/09/95	1. Interruption of accessory atrioventricular (AV) conduction pathways associated with tachycardia; 2. The treatment of AV nodal re-entrant tachycardia 3. Creation of complete AV nodal block in patients with a difficult to control ventricular response to an atrial arrhythmia 4. Intracardiac recording or stimulation	NR	4 mm tip electrode

NR=not reported in SSE or product catalogue

151

The characteristics and performance for this type of catheter are generally equivalent across manufacturers and the outcome data support that equivalence in that 18% of the study subjects were treated with non-study catheters and only 15% to 16% of the study procedures could be considered non-successful (see Section 8.6.3, Episode Reduction, Table F-29a and 29b).

Overall, bi-directional conduction block at the isthmus was achieved in the majority of the 89/95 subjects who received an isthmus line ablation (73/89, 82.0%, Table F-48), with the majority completed with the NavAblator™ only (30/34 subjects, 88.2%), or with non-study ("other") catheters (18/18, 100.0%).

Of equal interest is that the success in reducing the recurrence of symptomatic AF episodes appears to be without regard to whether or not "bi-directional conduction block" was reported for the isthmus line.

Table F-49, Successful Bi-Directional Conduction Block at Isthmus by Catheter

Catheters	Success Frequency/n	%
REVELATION Tx only	12/18*	66.7
NavAblator only	30/34	88.2
Other only	18/18	100.0
REVELATION Tx, Other	8/10	80.0
NavAblator, Other	3/5	60.0
REVELATION Tx, NavAblator	2/2	100.0
Isthmus line not ablated	6	-
Total	73/89	82.0

* 2 unspecified bi-directional block.

These data show that the NavAblator™ has been used to create the isthmus line, once it became available, more often than "standard institutional procedure" and that it is successful in creating bi-directional conduction block as often or more often than the "other" catheters.

It should be noted that the REVELATION® Tx was used to create a line of block at the isthmus in 13.5% of the time am isthmus lesion was incorporated into the procedure.

7.9 Related Clinical Studies

There were two other clinical studies conducted with the predecessor device, the Cardima PATHFINDER® AF, whose name was later changed to the REVELATION®. This device differed from the subject investigational device in that the REVELATION® does not incorporate temperature sensing thermocouples. In Europe a multi center study was conducted with this device, the results of which have been referenced in the prologue of the investigational plan, but for which there is limited access to raw data, so the results are not intended to support the safety and effectiveness for this device.

In addition, a single center/single investigator study of 29 subjects was conducted in the US, where the use of a non-temperature sensing device for the purpose of ablation in considered "off-label". This study has been published and the reprint is included with the bibliography supporting this PMA application. The results of this study demonstrate a 79% success rate, over a mean follow up of 19.7 months[10].

8.0 Conclusions

Based upon the results for the stated criteria, the safety and effectiveness of the Cardima REVELATION® Tx with NavAblator™ Ablation System has been successfully demonstrated.

References

1 Fuster and Rydén *et al*, *ACC/AHA/ESC Guidelines For The Management Of Patients With Atrial Fibrillation.* J Am Coll Cardiol 2001;38

2 Roy D, Talajic M, Dorian P, Connolly S et al., for the *Canadian Trial of Atrial Fibrillation Investigators.* N Engl J med 2000, 342:913-920.

3 Chaudhry GM, Haffajee, CI, *Algorithms Useful In The Treatment Of Atrial Fibrillation.* Curr Opin Cardiol 2002, 17:52-57.

4 Cox, JL, *et al. From Fisherman to Fibrillation: An Unbroken Line of Progress.* Ann Thorac Surg 1994;58:1269-73

5 Saksena S, et al. *Report of the NASPE/NHLBI Round Table on Future Research Directions in Atrial Fibrillation.* PACE 2001;24:1435-1452

6 Khot MB, *Atrial Fibrillation: An Overview.* Resident Research & Review. June 2002

7 Copyright pending. Used with permission from author: Paul Dorian, M.D., Professor of Medicine, Division of Cardiology, St. Michael's Hospital, Toronto, Ontario

8 Jumrussirikul P, et al. *Prospective Comparison of Lesions Created Using a Multipolar Microcatheter Ablation System with Those Created using a Pullback Approach with Standard Radiofrequency Ablation in the Canine Atrium.* PACE 2000; 23:203-213.

9 Gaita, F, et al. Catheter Ablation, Atrial Fibrillation [Chapter 16]. 1998 from Saoudi N, et al. *Atrial Flutter and Fibrillation: From Basic to Clinical Applications.* Armonk, NY: Future Publishing Co.

10 Kocheril, A. *Right Atrial Mapping and Linear Ablation for Paroxysmal Atrial Fibrillation.* Journal of Interventional Cardiac Electrophysiology. 2001;5:505-510.

11 Natale, A., et al. *Catheter Ablation Approach on the Right Side Only for Paroxysmal Atrial Fibrillation Therapy: Long-Term Results.* PACE. 2000;23:224-233.

12 Wellens, HJJ. *Pulmonary Vein Ablation in Atrail Fibrillation* (editorial). Circulation, 2000;102:2562-2564.

CARDIMA®

Protocol No. C-97-103-AF III
RF ABLATION

USE SEPARATE PAGE FOR EACH POSITION OR CHANGE OF CATHETER

Subject Initials [redacted] LI

Subject ID Number [redacted]

Date Performed 10 DD JAN MON 02 YR

Ablation catheters: ☑ REVELATION™ Tx ☐ NavAblator™

Building catheters: ☒ NAVIPORT® 10mm ☐ NAVIPORT® 30mm ☐ NAVIPORT® 40mm ☐ Other _____

Lesion Location: POS I ☒ A) IVC to SVC (posterolateral) ☐ B) SVC to IVC (posteroseptal) ☐ C) IVC to TA (isthmus) ☐ D) SVC to TA (anterior)

PAGE 1 OF 6

ABLATION DATA

	BIOPOLAR EGM AMPLITUDE PRE (mV)	RF ELECTRODE(S)	IMPEDANCE Rise >20 ohms	ACTUAL TEMP (°C)	DURATION (sec)	BIPOLAR EGM AMPLITUDE POST (mV)	SPLIT POTENTIAL	COAGULUM	COMMENTS Position changes and arrhythmias
1	0.1 ~~NA~~ 6/4/02 PB	1	☐ Yes	50	60	Sent to Cardima	☐ Yes	☐ Yes	High output pacing → ϕ stimulation
2	PB 6/4/02	2	☐ Yes	44	60		☐ Yes	☐ Yes	
3		3	☐ Yes	40	18		☐ Yes	☐ Yes	
4		3	☐ Yes	51	60		☐ Yes	☐ Yes	
5		4	☐ Yes	51	60		☐ Yes	☐ Yes	
6		5	☐ Yes	50	60		☐ Yes	☐ Yes	
7		6	☐ Yes	51	60		☐ Yes	☐ Yes	
8		7	☐ Yes	51	60	0.1 PB 6/4/02	☐ Yes	☐ Yes	
9			☐ Yes				☐ Yes	☐ Yes	
10			☐ Yes				☐ Yes	☐ Yes	
11			☐ Yes				☐ Yes	☐ Yes	
12			☐ Yes				☐ Yes	☐ Yes	
13			☐ Yes				☐ Yes	☐ Yes	
14			☐ Yes				☐ Yes	☐ Yes	
15			☐ Yes				☐ Yes	☐ Yes	
16			☐ Yes				☐ Yes	☐ Yes	
17			☐ Yes				☐ Yes	☐ Yes	
18			☐ Yes				☐ Yes	☐ Yes	
19			☐ Yes				☐ Yes	☐ Yes	
20			☐ Yes				☐ Yes	☐ Yes	

COMPLETE ALL ITEMS. ITEMS MISSING OR INCONSISTENT WILL REQUIRE ADDITIONAL FOLLOW-UP.

CARDIMA®

ɪtocol No. C-97-103-AF III
RF ABLATION

USE SEPARATE PAGE FOR EACH POSITION OR CHANGE OF CATHETER

Subjec Initial [redacted] Subjec ID Numbe [redacted]

Date Performed 1 0 DD J A N MON 0 2 YR

Ablation catheters: ☑ REVELATION™ Tx ☐ NavAblator™

Building catheters: ☒ NAVIPORT® 10mm ☐ NAVIPORT® 30mm ☐ NAVIPORT® 40mm ☐ Other _____

Lesion Location: ☒ A) IVC to SVC (posterolateral) ☐ B) SVC to IVC (posteroseptal) ☐ C) IVC to TA (isthmus) ☐ D) SVC to TA (anterior)

PAGE 1 OF 6

ABLATION DATA

	BIOPOLAR EGM AMPLITUDE PRE (mV)	RF ELECTRODE(S)	IMPEDANCE Rise >20 ohms	ACTUAL TEMP (°C)	DURATION (sec)	BIPOLAR EGM AMPLITUDE POST (mV)	SPLIT POTENTIAL	COAGULUM	COMMENTS Position changes and arrhythmias
1	NA	1	☐ Yes	50	60	Sent to Cardima	☐ Yes	☐ Yes	High output pacing → ϕ stimulation
2	↓	2	☐ Yes	49	60	↓	☐ Yes	☐ Yes	
3		3	☐ Yes	40	18		☐ Yes	☐ Yes	
4		3	☐ Yes	51	60		☐ Yes	☐ Yes	
5		4	☐ Yes	51	60		☐ Yes	☐ Yes	
6		5	☐ Yes	50	60		☐ Yes	☐ Yes	
7		6	☐ Yes	51	60		☐ Yes	☐ Yes	
8		7	☐ Yes	51	60		☐ Yes	☐ Yes	
9			☐ Yes				☐ Yes	☐ Yes	
10			☐ Yes				☐ Yes	☐ Yes	
11			☐ Yes				☐ Yes	☐ Yes	
12			☐ Yes				☐ Yes	☐ Yes	
13			☐ Yes				☐ Yes	☐ Yes	
14			☐ Yes				☐ Yes	☐ Yes	
15			☐ Yes				☐ Yes	☐ Yes	
16			☐ Yes				☐ Yes	☐ Yes	
17			☐ Yes				☐ Yes	☐ Yes	
18			☐ Yes				☐ Yes	☐ Yes	
19			☐ Yes				☐ Yes	☐ Yes	
20			☐ Yes				☐ Yes	☐ Yes	

COMPLETE ALL ITEMS. ITEMS MISSING OR INCONSISTENT WILL REQUIRE ADDITIONAL FOLLOW-UP.

CARDIMA®

Protocol No. C-97-103-AF III
RF ABLATION

USE SEPARATE PAGE FOR EACH POSITION OR CHANGE OF CATHETER

Subject Initials: [redacted] Subject ID Number: [redacted]

Date Performed: DD 10 MON JAN 02 YR

Ablation catheters: ☒ REVELATION™ Tx ☐ NavAblator™

Building catheters: ☒ NAVIPORT® 10mm ☐ NAVIPORT® 30mm ☐ NAVIPORT® 40mm ☐ Other _____

Lesion Location: ☒ A) IVC to SVC (posterolateral) ☐ B) SVC to IVC (posteroseptal) ☐ C) IVC to TA (isthmus) ☐ D) SVC to TA (anterior)

PAGE 2 OF 6

ABLATION DATA

	BIOPOLAR EGM AMPLITUDE PRE (mV)	RF ELECTRODE(S)	IMPEDANCE Rise >20 ohms	ACTUAL TEMP (°C)	DURATION (sec)	BIPOLAR EGM AMPLITUDE POST (mV)	SPLIT POTENTIAL	COAGULUM	COMMENTS Position changes and arrhythmias
1	NA	1	☐ Yes	50	60	NA	☐ Yes	☐ Yes	
2		1	☐ Yes	51	60		☐ Yes	☐ Yes	
3		2	☐ Yes	48	60		☐ Yes	☐ Yes	
4		2	☐ Yes	50	60		☐ Yes	☐ Yes	
5		1	☐ Yes	50	60		☐ Yes	☐ Yes	
6		2	☐ Yes	48	60		☐ Yes	☐ Yes	
7		3	☐ Yes	51	60		☐ Yes	☐ Yes	
8		4	☒ Yes	40	20		☐ Yes	☐ Yes	
9		4	☒ Yes	37	14		☐ Yes	☐ Yes	
10		5	☐ Yes	49	60		☐ Yes	☐ Yes	
11		6	☐ Yes	50	60		☐ Yes	☐ Yes	
12		7	☐ Yes	48	60		☐ Yes	☐ Yes	
13		8	☐ Yes	48	60		☐ Yes	☒ Yes	Elect: 1-2-4 → mod. 3 heavy
14			☐ Yes				☐ Yes	☐ Yes	5-6-7-8 → Small
15			☐ Yes				☐ Yes	☐ Yes	
16			☐ Yes				☐ Yes	☐ Yes	
17			☐ Yes				☐ Yes	☐ Yes	
18			☐ Yes				☐ Yes	☐ Yes	
19			☐ Yes				☐ Yes	☐ Yes	
20			☐ Yes				☐ Yes	☐ Yes	

COMPLETE ALL ITEMS. ITEMS MISSING OR INCONSISTENT WILL REQUIRE ADDITIONAL FOLLOW-UP.

CARDIMA

tocol No. C-97-103-AF III
RF ABLATION

USE SEPARATE PAGE FOR EACH POSITION OR CHANGE OF CATHETER

Subject Initials

Subject ID Number

Date Performed 10 DD JAN MON 02 YR

Ablation catheters: ☒ REVELATION™ Tx ☐ NavAblator™

Building catheters: ☒ NAVIPORT® 10mm ☐ NAVIPORT® 30mm ☐ NAVIPORT® 40mm ☐ Other

Lesion Location: ☒ A) IVC to SVC (posterolateral) ☐ B) SVC to IVC (posteroseptal) ☐ C) IVC to TA (isthmus) ☐ D) SVC to TA (anterior)

PAGE 2 OF 6

ABLATION DATA

	BIPOLAR EGM AMPLITUDE PRE (mV)	RF ELECTRODE(S)	IMPEDANCE Rise >20 ohms	ACTUAL TEMP (°C)	DURATION (sec)	BIPOLAR EGM AMPLITUDE POST (mV)	SPLIT POTENTIAL	COAGULUM	COMMENTS Position changes and arrhythmias
1	0.1 mV 6/11/02 TB	1	☐ Yes	50	60	NA	☐ Yes	☐ Yes	
2		1	☐ Yes	51	60		☐ Yes	☐ Yes	
3		2	☐ Yes	48	60		☐ Yes	☐ Yes	
4		2	☐ Yes	50	60		☐ Yes	☐ Yes	
5		1	☐ Yes	50	60		☐ Yes	☐ Yes	
6		2	☐ Yes	48	60		☐ Yes	☐ Yes	
7		3	☐ Yes	51	60		☐ Yes	☐ Yes	
8		4	☒ Yes	40	20		☐ Yes	☐ Yes	
9		4	☒ Yes	37	14		☐ Yes	☐ Yes	
10		5	☐ Yes	49	60		☐ Yes	☐ Yes	
11		6	☐ Yes	50	60		☐ Yes	☐ Yes	
12		7	☐ Yes	48	60		☐ Yes	☐ Yes	
13		8	☐ Yes	48	60	0.05 TB 6/11/02	☐ Yes	☒ Yes	Elect: 1-2-4 → mod. 3 heavy 5-6-7-8 → Small
14			☐ Yes				☐ Yes	☐ Yes	
15			☐ Yes				☐ Yes	☐ Yes	
16			☐ Yes				☐ Yes	☐ Yes	
17			☐ Yes				☐ Yes	☐ Yes	
18			☐ Yes				☐ Yes	☐ Yes	
19			☐ Yes				☐ Yes	☐ Yes	
20			☐ Yes				☐ Yes	☐ Yes	

COMPLETE ALL ITEMS. ITEMS MISSING OR INCONSISTENT WILL REQUIRE ADDITIONAL FOLLOW-UP.

CARDIMA®

Protocol No. C-97-103-AF III
RF ABLATION

USE SEPARATE PAGE FOR EACH POSITION OR CHANGE OF CATHETER

Subject Initials: [redacted] LI Subject ID Number: [redacted]

Date Performed: DD 10 MON 04 YR 02

Ablation catheters: ☒ REVELATION™ Tx ☐ NavAblator™

Building catheters: ☒ NAVIPORT® 10mm ☐ NAVIPORT® 30mm ☐ NAVIPORT® 40mm ☐ Other _____

Lesion Location: ☐ A) IVC to SVC (posterolateral) ☒ B) SVC to IVC (posteroseptal) ☐ C) IVC to TA (isthmus) ☐ D) SVC to TA (anterior)

OSI

PAGE 3 OF 6

ABLATION DATA

	BIOPOLAR EGM AMPLITUDE PRE (mV)	RF ELECTRODE(S)	IMPEDANCE Rise >20 ohms	ACTUAL TEMP (°C)	DURATION (sec)	BIPOLAR EGM AMPLITUDE POST (mV)	SPLIT POTENTIAL	COAGULUM	COMMENTS Position changes and arrhythmias
1	0.1 mV 6/11/02	1	☐ Yes	50	60	–	☐ Yes	☐ Yes	
2	–	2	☐ Yes	50	60	–	☐ Yes	☐ Yes	
3	–	3	☐ Yes	49	60	–	☐ Yes	☐ Yes	
4	–	4	☐ Yes	50	60	–	☐ Yes	☐ Yes	
5	–	5	☐ Yes	49	60		☐ Yes	☐ Yes	
6	–	6	☐ Yes	49	60	0.1 mV 6/11/02	☐ Yes	☐ Yes	
7			☐ Yes				☐ Yes	☐ Yes	
8			☐ Yes				☐ Yes	☐ Yes	
9			☐ Yes				☐ Yes	☐ Yes	
10			☐ Yes				☐ Yes	☐ Yes	
11			☐ Yes				☐ Yes	☐ Yes	
12			☐ Yes				☐ Yes	☐ Yes	
13			☐ Yes				☐ Yes	☐ Yes	
14			☐ Yes				☐ Yes	☐ Yes	
15			☐ Yes				☐ Yes	☐ Yes	
16			☐ Yes				☐ Yes	☐ Yes	
17			☐ Yes				☐ Yes	☐ Yes	
18			☐ Yes				☐ Yes	☐ Yes	
19			☐ Yes				☐ Yes	☐ Yes	
20			☐ Yes				☐ Yes	☐ Yes	

COMPLETE ALL ITEMS. ITEMS MISSING OR INCONSISTENT WILL REQUIRE ADDITIONAL FOLLOW-UP.

CARDIMA

Protocol No. C-97-103-AF III
RF ABLATION

USE SEPARATE PAGE FOR EACH POSITION OR CHANGE OF CATHETER

Subject Initials: [redacted]
Subject ID Number: [redacted]
Date Performed: 10 DD 74 MON 02 YR

Ablation catheters: ☒ REVELATION™ Tx ☐ NavAblator™
Building catheters: ☒ NAVIPORT® 10mm ☐ NAVIPORT® 30mm ☐ NAVIPORT® 40mm ☐ Other _____
Lesion Location: ☐ A) IVC to SVC (posterolateral) ☒ B) SVC to IVC (posteroseptal) ☐ C) IVC to TA (isthmus) ☐ D) SVC to TA (anterior)

PAGE 3 OF 6

ABLATION DATA

	BIOPOLAR EGM AMPLITUDE PRE (mV)	RF ELECTRODE(S)	IMPEDANCE Rise >20 ohms	ACTUAL TEMP (°C)	DURATION (sec)	BIPOLAR EGM AMPLITUDE POST (mV)	SPLIT POTENTIAL	COAGULUM	COMMENTS Position changes and arrhythmias
1		1	☐ Yes	50	60		☐ Yes	☐ Yes	
2		2	☐ Yes	50	60		☐ Yes	☐ Yes	
3		3	☐ Yes	49	60		☐ Yes	☐ Yes	
4		4	☐ Yes	50	60		☐ Yes	☐ Yes	
5		5	☐ Yes	49	60		☐ Yes	☐ Yes	
6		6	☐ Yes	49	66		☐ Yes	☐ Yes	
7			☐ Yes				☐ Yes	☐ Yes	
8			☐ Yes				☐ Yes	☐ Yes	
9			☐ Yes				☐ Yes	☐ Yes	
10			☐ Yes				☐ Yes	☐ Yes	
11			☐ Yes				☐ Yes	☐ Yes	
12			☐ Yes				☐ Yes	☐ Yes	
13			☐ Yes				☐ Yes	☐ Yes	
14			☐ Yes				☐ Yes	☐ Yes	
15			☐ Yes				☐ Yes	☐ Yes	
16			☐ Yes				☐ Yes	☐ Yes	
17			☐ Yes				☐ Yes	☐ Yes	
18			☐ Yes				☐ Yes	☐ Yes	
19			☐ Yes				☐ Yes	☐ Yes	
20			☐ Yes				☐ Yes	☐ Yes	

COMPLETE ALL ITEMS. ITEMS MISSING OR INCONSISTENT WILL REQUIRE ADDITIONAL FOLLOW-UP.

CARDIMA®

Protocol No. C-97-103-AF III
RF ABLATION

USE SEPARATE PAGE FOR EACH POSITION OR CHANGE OF CATHETER

Subject Initials [redacted] LI Subject ID Number [redacted]

Date Performed 10 DD JAN MON 02 YR

Ablation catheters: ☒ REVELATION™ Tx ☐ NavAblator™

Building catheters: ☒ NAVIPORT® 10mm ☐ NAVIPORT® 30mm ☐ NAVIPORT® 40mm ☐ Other _____

Lesion Location: ☐ A) IVC to SVC (posterolateral) ☒ B) SVC to IVC (posteroseptal) ☐ C) IVC to TA (isthmus) ☐ D) SVC to TA (anterior)

POST

PAGE 4 OF 6

ABLATION DATA

	BIOPOLAR EGM AMPLITUDE PRE (mV)	RF ELECTRODE(S)	IMPEDANCE Rise >20 ohms	ACTUAL TEMP (°C)	DURATION (sec)	BIPOLAR EGM AMPLITUDE POST (mV)	SPLIT POTENTIAL	COAGULUM	COMMENTS Position changes and arrhythmias
1	0.2 NA	1	☐ Yes	49	60	NA	☐ Yes	☐ Yes	
2		2	☐ Yes	50	60		☐ Yes	☐ Yes	
3		3	☐ Yes	49	60		☐ Yes	☐ Yes	
4		4	☐ Yes	50	60		☐ Yes	☐ Yes	A-fib
5		5	☐ Yes	51	60		☐ Yes	☐ Yes	
6		6	☐ Yes	50	60	0.2	☐ Yes	☐ Yes	Spont → NSR
7			☐ Yes			deviation	☐ Yes	☐ Yes	
8			☐ Yes				☐ Yes	☐ Yes	
9			☐ Yes				☐ Yes	☐ Yes	
10			☐ Yes				☐ Yes	☐ Yes	
11			☐ Yes				☐ Yes	☐ Yes	
12			☐ Yes				☐ Yes	☐ Yes	
13			☐ Yes				☐ Yes	☐ Yes	
14			☐ Yes				☐ Yes	☐ Yes	
15			☐ Yes				☐ Yes	☐ Yes	
16			☐ Yes				☐ Yes	☐ Yes	
17			☐ Yes				☐ Yes	☐ Yes	
18			☐ Yes				☐ Yes	☐ Yes	
19			☐ Yes				☐ Yes	☐ Yes	
20			☐ Yes				☐ Yes	☐ Yes	

COMPLETE ALL ITEMS. ITEMS MISSING OR INCONSISTENT WILL REQUIRE ADDITIONAL FOLLOW-UP.

CARDIMA

tocol No. C-97-103-AF III
RF ABLATION

USE SEPARATE PAGE FOR EACH POSITION OR CHANGE OF CATHETER

Subject Initials [redacted] Subje ID Numb [redacted]

Date Performed 10 DD JAN MON 02 YR

Ablation catheters: ☒ REVELATION™ Tx ☐ NavAblator™

Building catheters: ☒ NAVIPORT® 10mm ☐ NAVIPORT® 30mm ☐ NAVIPORT® 40mm ☐ Other _____

Lesion Location: ☐ A) IVC to SVC (posterolateral) ☒ B) SVC to IVC (posteroseptal) ☐ C) IVC to TA (isthmus) ☐ D) SVC to TA (anterior)

PAGE 4 OF 6

ABLATION DATA

	BIOPOLAR EGM AMPLITUDE PRE (mV)	RF ELECTRODE(S)	IMPEDANCE Rise >20 ohms	ACTUAL TEMP (°C)	DURATION (sec)	BIPOLAR EGM AMPLITUDE POST (mV)	SPLIT POTENTIAL	COAGULUM	COMMENTS Position changes and arrhythmias
1	NA	1	☐ Yes	49	60	NA	☐ Yes	☐ Yes	
2		2	☐ Yes	50	60		☐ Yes	☐ Yes	
3		3	☐ Yes	49	60		☐ Yes	☐ Yes	
4		4	☐ Yes	50	60		☐ Yes	☐ Yes	A-fib
5		5	☐ Yes	51	60		☐ Yes	☐ Yes	
6		6	☐ Yes	50	60		☐ Yes	☐ Yes	Spont → NSR
7			☐ Yes				☐ Yes	☐ Yes	
8			☐ Yes				☐ Yes	☐ Yes	
9			☐ Yes				☐ Yes	☐ Yes	
10			☐ Yes				☐ Yes	☐ Yes	
11			☐ Yes				☐ Yes	☐ Yes	
12			☐ Yes				☐ Yes	☐ Yes	
13			☐ Yes				☐ Yes	☐ Yes	
14			☐ Yes				☐ Yes	☐ Yes	
15			☐ Yes				☐ Yes	☐ Yes	
16			☐ Yes				☐ Yes	☐ Yes	
17			☐ Yes				☐ Yes	☐ Yes	
18			☐ Yes				☐ Yes	☐ Yes	
19			☐ Yes				☐ Yes	☐ Yes	
20			☐ Yes				☐ Yes	☐ Yes	

COMPLETE ALL ITEMS. ITEMS MISSING OR INCONSISTENT WILL REQUIRE ADDITIONAL FOLLOW-UP.

CARDIMA

Protocol No. C-97-103-AF III
AF ABLATION

USE SEPARATE PAGE FOR EACH POSITION OR CHANGE OF CATHETER

Subject Initial: [redacted]
Subject ID Number: [redacted]
Date Performed: DD 10 JAN MON 02 YR

Ablation catheters: ☒ REVELATION™ Tx ☐ NavAblator™
Building catheters: ☒ NAVIPORT® 10mm ☐ NAVIPORT® 30mm ☐ NAVIPORT® 40mm ☐ Other _____
Lesion Location: ☐ A) IVC to SVC (posterolateral) ☒ B) SVC to IVC (posteroseptal) ☐ C) IVC to TA (isthmus) ☐ D) SVC to TA (anterior)

PAGE 5 OF 6

ABLATION DATA

	BIOPOLAR EGM AMPLITUDE PRE (mV)	RF ELECTRODE(S)	IMPEDANCE Rise >20 ohms	ACTUAL TEMP (°C)	DURATION (sec)	BIPOLAR EGM AMPLITUDE POST (mV)	SPLIT POTENTIAL	COAGULUM	COMMENTS Position changes and arrhythmias
1	ND duration	2	☐ Yes	50	66		☐ Yes	☐ Yes	
2		3	☐ Yes	49	60		☐ Yes	☐ Yes	
3		4	☐ Yes	50	60		☐ Yes	☐ Yes	
4		5	☒ Yes	50	60		☐ Yes	☐ Yes	
5		6	☐ Yes	49	60	0.2	☐ Yes	☒ Yes	sm → 1-2-5-6-7-8 med 3-4
6			☐ Yes				☐ Yes	☐ Yes	
7			☐ Yes				☐ Yes	☐ Yes	
8			☐ Yes				☐ Yes	☐ Yes	
9			☐ Yes				☐ Yes	☐ Yes	
10			☐ Yes				☐ Yes	☐ Yes	
11			☐ Yes				☐ Yes	☐ Yes	
12			☐ Yes				☐ Yes	☐ Yes	
13			☐ Yes				☐ Yes	☐ Yes	
14			☐ Yes				☐ Yes	☐ Yes	
15			☐ Yes				☐ Yes	☐ Yes	
16			☐ Yes				☐ Yes	☐ Yes	
17			☐ Yes				☐ Yes	☐ Yes	
18			☐ Yes				☐ Yes	☐ Yes	
19			☐ Yes				☐ Yes	☐ Yes	
20			☐ Yes				☐ Yes	☐ Yes	

COMPLETE ALL ITEMS. ITEMS MISSING OR INCONSISTENT WILL REQUIRE ADDITIONAL FOLLOW-UP.

CARDIMA®

tocol No. C-97-103-AF III
HF ABLATION

USE SEPARATE PAGE FOR EACH POSITION OR CHANGE OF CATHETER

Subject Initials ____ ____ ____

Subje ID Numb

Date Performed 1 0 DD J A N MON 0 2 YR

Ablation catheters: ☒ REVELATION™ Tx ☐ NavAblator™

Building catheters: ☒ NAVIPORT® 10mm ☐ NAVIPORT® 30mm ☐ NAVIPORT® 40mm ☐ Other _____

Lesion Location: ☐ A) IVC to SVC (posterolateral) ☒ B) SVC to IVC (posteroseptal) ☐ C) IVC to TA (isthmus) ☐ D) SVC to TA (anterior)

PAGE 5 OF 6

ABLATION DATA

	BIOPOLAR EGM AMPLITUDE PRE (mV)	RF ELECTRODE(S)	IMPEDANCE Rise >20 ohms	ACTUAL TEMP (°C)	DURATION (sec)	BIPOLAR EGM AMPLITUDE POST (mV)	SPLIT POTENTIAL	COAGULUM	COMMENTS Position changes and arrhythmias
1		2	☐ Yes	50	60		☐ Yes	☐ Yes	
2		3	☐ Yes	49	60		☐ Yes	☐ Yes	
3		4	☐ Yes	50	60		☐ Yes	☐ Yes	
4		5	☒ Yes	50	60		☐ Yes	☐ Yes	
5		6	☐ Yes	49	60		☐ Yes	☒ Yes	Bm → 1-2-5-6-7-8 mod 3-4
6			☐ Yes				☐ Yes	☐ Yes	
7			☐ Yes				☐ Yes	☐ Yes	
8			☐ Yes				☐ Yes	☐ Yes	
9			☐ Yes				☐ Yes	☐ Yes	
10			☐ Yes				☐ Yes	☐ Yes	
11			☐ Yes				☐ Yes	☐ Yes	
12			☐ Yes				☐ Yes	☐ Yes	
13			☐ Yes				☐ Yes	☐ Yes	
14			☐ Yes				☐ Yes	☐ Yes	
15			☐ Yes				☐ Yes	☐ Yes	
16			☐ Yes				☐ Yes	☐ Yes	
17			☐ Yes				☐ Yes	☐ Yes	
18			☐ Yes				☐ Yes	☐ Yes	
19			☐ Yes				☐ Yes	☐ Yes	
20			☐ Yes				☐ Yes	☐ Yes	

COMPLETE ALL ITEMS. ITEMS MISSING OR INCONSISTENT WILL REQUIRE ADDITIONAL FOLLOW-UP.

CARDIMA®

tocol No. C-97-103-AF III
HF ABLATION

USE SEPARATE PAGE FOR EACH POSITION OR CHANGE OF CATHETER

Subjec Initial: [redacted]

Subjec ID Numbe [redacted]

Date Performed 10 DD JAN MON 02 YR

Ablation catheters: ☒ REVELATION™ Tx ☒ NavAblator™

Building catheters: ☐ NAVIPORT® 10mm ☐ NAVIPORT® 30mm ☐ NAVIPORT® 40mm ☐ Other _____

Lesion Location: ☐ A) IVC to SVC (posterolateral) ☐ B) SVC to IVC (posteroseptal) ☒ C) IVC to TA (isthmus) ☐ D) SVC to TA (anterior)

PAGE 6 OF 6

ABLATION DATA

	BIOPOLAR EGM AMPLITUDE PRE (mV)	RF ELECTRODE(S)	IMPEDANCE Rise >20 ohms	ACTUAL TEMP (°C)	DURATION (sec)	BIPOLAR EGM AMPLITUDE POST (mV)	SPLIT POTENTIAL	COAGULUM	COMMENTS Position changes and arrhythmias
1	NA	1	☐ Yes	48	60	NA	☐ Yes	☐ Yes	Attempt to use Revelation for
2		1	☐ Yes	53	60		☐ Yes	☐ Yes	Isthmus line not successful
3		1	☐ Yes	50	60		☐ Yes	☐ Yes	Δ to NavAblator c drag burns.
4		1	☐ Yes	52	60		☐ Yes	☐ Yes	
5		1	☐ Yes	52	60		☐ Yes	☐ Yes	
6		1	☐ Yes	49	60		☐ Yes	☐ Yes	
7		1	☐ Yes	55	~~60~~ 55		☐ Yes	☐ Yes	
8		+ 1	☐ Yes		~~55~~		☐ Yes	☐ Yes	Pace from prox CS → ⊕ block
9			☐ Yes				☐ Yes	☐ Yes	Biosense map done → ⊕ block.
10			☐ Yes				☐ Yes	☐ Yes	
11			☐ Yes				☐ Yes	☐ Yes	
12			☐ Yes				☐ Yes	☐ Yes	
13			☐ Yes				☐ Yes	☐ Yes	
14			☐ Yes				☐ Yes	☐ Yes	
15			☐ Yes				☐ Yes	☐ Yes	
16			☐ Yes				☐ Yes	☐ Yes	
17			☐ Yes				☐ Yes	☐ Yes	
18			☐ Yes				☐ Yes	☐ Yes	
19			☐ Yes				☐ Yes	☐ Yes	
20			☐ Yes				☐ Yes	☐ Yes	

COMPLETE ALL ITEMS. ITEMS MISSING OR INCONSISTENT WILL REQUIRE ADDITIONAL FOLLOW-UP.

C-97-103 AF Rev. 7/1/2001

a. Massachusetts General Hospital

This study of seven goats conducted in the animal research facility at Massachusetts General Hospital under the direction of David Keane, MD, Ph.D. A key objective was to evaluate the effective set temperature range as well as device performance. Four trajectories in the right atrium were targeted, using an inferior approach. Ablation was performed with all electrodes at that site. No attempt was made to reposition the catheter and reapply RF after the initial ablation. In other words, no attempt was made to extend or connect ablation lines. Three animals were acute studies temperature was increased from 45°C to 50°C. In the third acute animal the lesions appeared to be better defined, so it was decided to continue the study at that set temperature four chronic studies, analyzing the lesion healing over a period of 4 weeks. A complete summary of the study of all seven goats follows.

Methodology

Each goat was maintained on anesthesia with Halothane via a respirator. The electrode catheter was then inserted through a guiding catheter via femoral percutaneous access into the right atrium of the goat. A number of pre-determined anatomic trajectories were targeted as the site of ablation throughout the study. Upon positioning the electrode catheter against the tissue in one of the specified trajectories, bipolar pacing thresholds and bipolar and unipolar electrograms were recorded. Radiofrequency energy was delivered through each electrode sequentially using a pre-defined thermocouple set temperature to provide feedback control of the RF power. The thermocouple positioned just proximal to the electrode was used for the feedback control. The initial settings were a 45°C set temperature and a 50W upper power limit. The differential impedance shutoff setting was set initially at 10Ω meaning that the RF generator will shut off if the impedance rises by more than 10Ω from the lowest impedance value throughout the run. Upon completion of radiofrequency energy delivery at all the trajectories, pacing thresholds and electrograms were again recorded.

At the conclusion of each procedure, the goat was either sacrificed acutely or survived for between 1 and 4 weeks. Upon sacrifice the heart was removed and examined for signs of trauma or other complications. Excised hearts were stored in formalin until

histological preparations were performed. H&E and Trichrome stains were used. Sections were taken transversely along the length of the lesion in 2 mm increments.

Results

Procedure Execution

The first three goats were sacrificed acutely. The remaining four goats were sacrificed at one-week intervals after the procedure up to 4 weeks. The first two were ablated with a control set temperature of 45°C. Because this temperature setting did not appear to produce adequate lesions, the set temperature was increased to 50°C for the remaining goats studied. The control settings were such that the RF generator would deliver power up to a maximum of 50W to achieve the desired set temperature. During the course of the first five goats studied, it was observed that the power would at times rise to the 50 W maximum without achieving the set temperature. It was presumed that this occurred because the electrode was in poor tissue contact. In order to reduce the likelihood of thrombus formation when the electrode was not in contact, the maximum RF power limit was reduced to 25W for the remaining two animals studied. During the course of the study the differential impedance cutoff limit was initially set to 10Ω. In some instances, this had to be increased to 20Ω or 30Ω because of fluctuations in impedance (presumably due to mechanical motion) that would cause the RF generator to shutoff within the first 5 seconds of RF delivery. For the procedure on Goat 56, after completion of the right atrial burns, a transseptal puncture was made and a transseptal sheath placed into the left atrium. RF energy applications were made in the left atrium outside the scope of the protocol and the results are not included. No acute complications resulted. Goat 55 expired during RF delivery along the IVC-TA isthmus. There was no evidence of mechanical cardiac trauma or damage to the AV node, leaving the cause as inconclusive. The procedural key points are summarized in **Table C-2**

Table C-2: Procedural Summary

Ref #	Goat ID #	Survival Duration	Control Set Temperature (°C)	Maximum Power (W)
1	54	Acute	45	50
2	55	Acute	45	50
3	56	Acute	50	50
4	57	1 week	50	50
5	61	2 weeks	50	25
6	62	3 weeks	50	25
7	58	4 weeks	50	50

Contact Assessment

Electrogram amplitudes and bipolar pacing thresholds were measured pre- and post-ablation. Absolute values of electrogram amplitudes from study to study cannot be compared because of possible variations in gain adjustments; however, they remain a good indicator of relative changes within a study. An example of electrograms obtained in study are presented in **Figure C-1**.

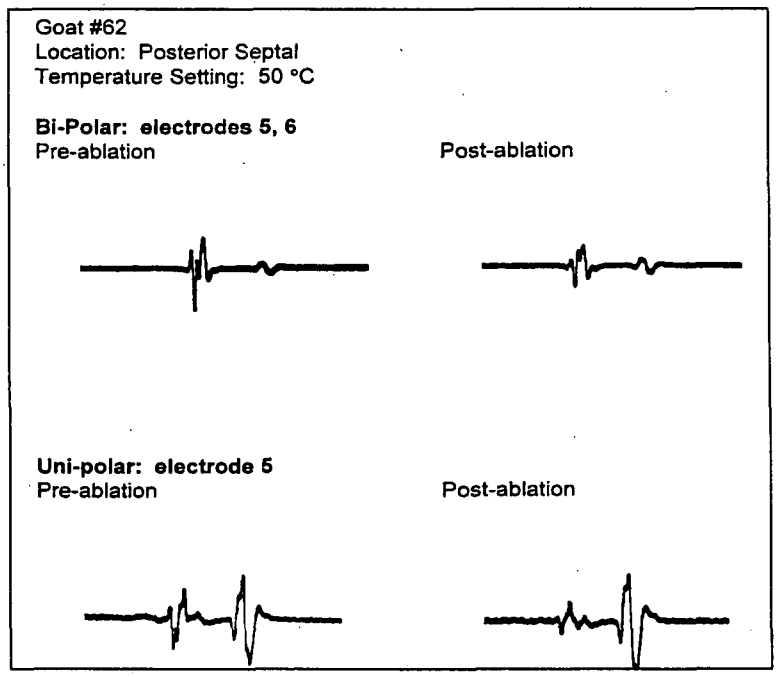


Figure C-1: Example of Bipolar and Unipolar Electrograms Pre- and Post-Ablation

The frequency and amount that the electrogram amplitudes decreased after RF ablation is shown in **Figure C-2.** Bipolar electrograms were reduced by more than 50% 36% of the time. Unipolar electrograms were reduced by more than 50% 23% of the time.

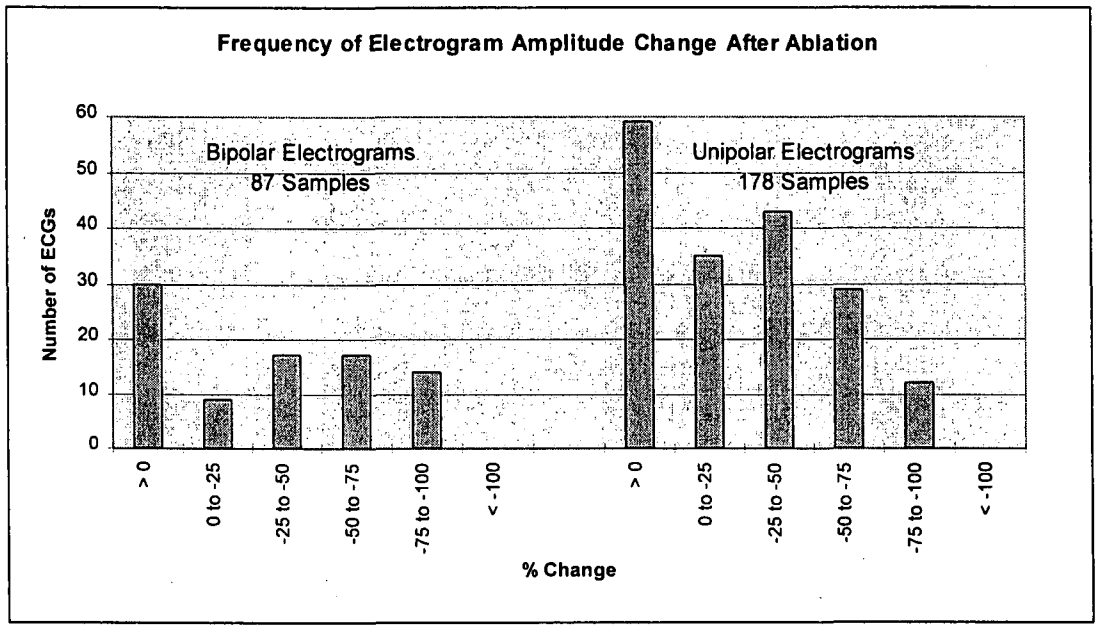


Figure C-2: Frequency of Electrogram Amplitude Change After Ablation

Figure C-3 shows the percentage of the time that pre-ablation pacing thresholds fell within a given range and what effect ablation had on the increase in the post-ablation threshold. A pre-ablation pacing threshold of less than 1.5 mA was achieved 35% of the time and resulted in a average pacing threshold increase of 146%.

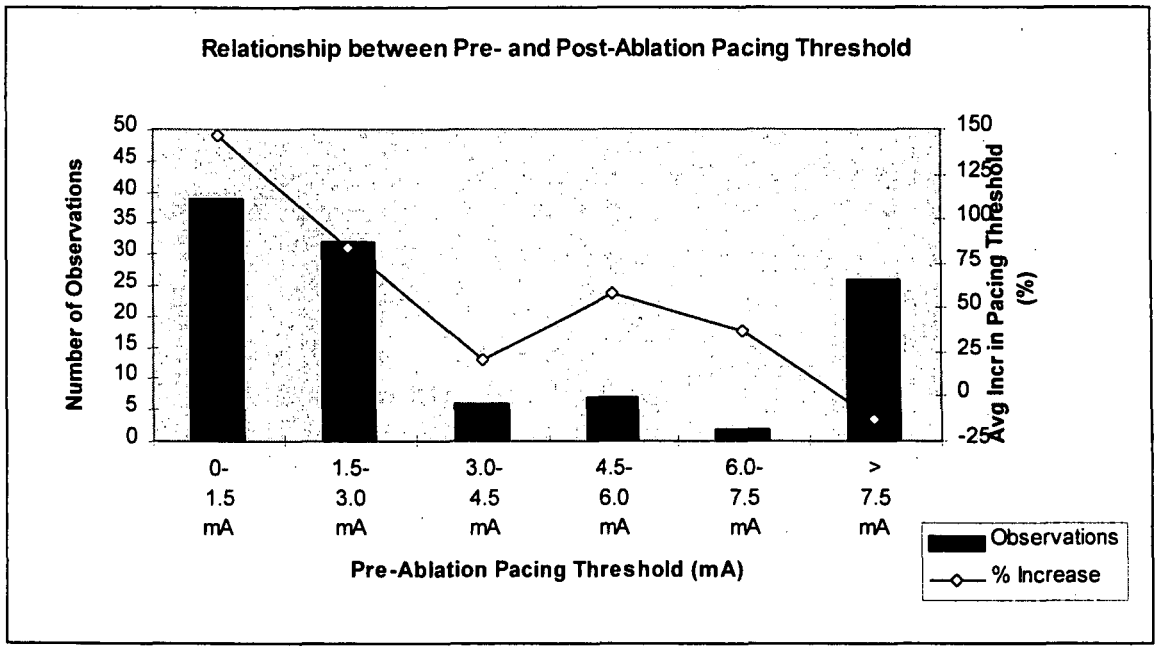


Figure C-3: Relationship between Pre- and Post-Ablation Pacing Thresholds

RF Power Delivery

The RF generator automatically adjusts RF power to maintain a constant temperature at the thermocouple. The average amount of RF power delivered by the RF generator to a given electrode varied throughout the study. Again, while the first five procedures were done at a setting of 50W maximum, the last two at 25W maximum.

Acute Coagulum Formation

After RF power delivery at each position, the catheter was removed and inspected for the presence of coagulum adhering to the electrodes. Grading the amount of coagulum is difficult and usually it was noted as present or not present on a given electrode. No abrupt impedance rises (i.e., sudden jumps to 200+Ω) were noted during any of the RF applications, keeping in mind that the differential impedance value was often increased to 20-30Ω to prevent shutoffs due to mechanical motion. The frequency of coagulum formation on the electrode is displayed as a function of power in **Figure C-4** (please note presence of coagulum = 10, no coagulum = 0). This illustration suggests no clear correlation between RF power and coagulum formation.

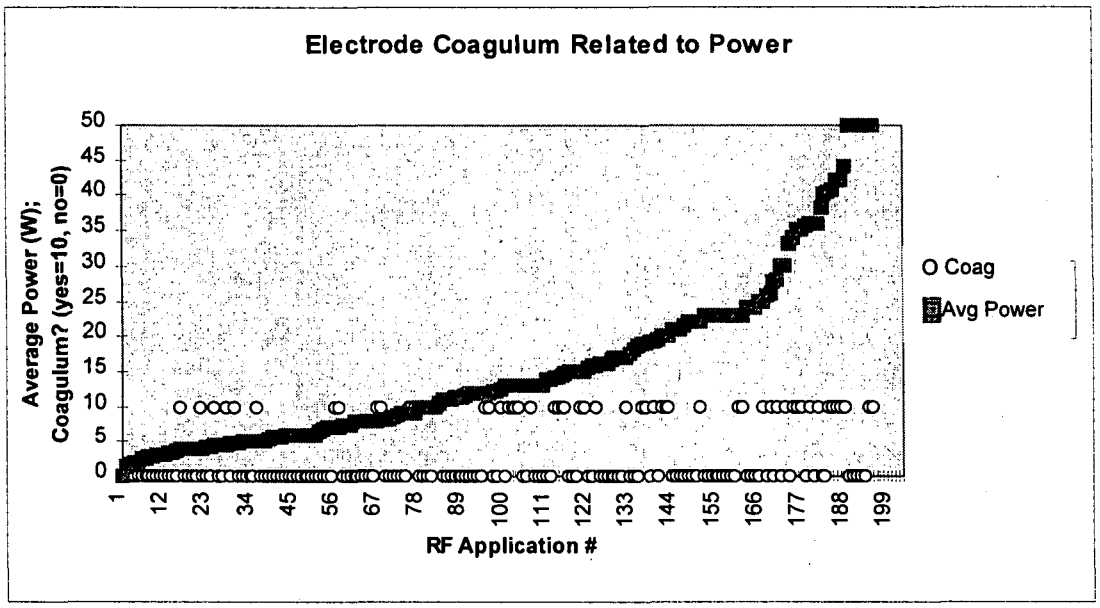


Figure C-4: Electrode Coagulum Related to Power

Gross Examinations

As mentioned above, Goat 55 expired during the final RF application along the IVC-TA isthmus. Only cardiac gross dissections were performed in this study, so distal infarcts, or evidence of embolic phenomena were not detected. However, the AV node of Goat 55 was examined by the pathologist and was determined to be

undamaged (not inadvertently ablated). An adherent thrombus approximately 14mm long was found on gross examination of the right atrium of Goat 55. There was no clinical indication of pulmonary embolization (i.e., rapid onset sinus tachycardia and drop in blood pressure) in this or any other animal. No mechanical trauma was noted in any of the animals studied, including Goat 55, except as caused by the intended transseptal puncture in Goat 56.

Table C-3 shows the intended ablation locations where the pathologist was able to identify lesions. Lesions were identified at 15 trajectories of the 28 attempted (54%) in all goats. For the 50°C set temperature, lesions were identified at 12 trajectories of 20 attempted (60%). The anterior lesion in Goat 54 may have been overlooked by the pathologist.

Table C-3: Summary of Lesions Identified Pathologically

Ref #	Goat ID#	IVC-SVC	Septal	Anterior	IVC-TA
1	54	x	x	?	x
2	55				
3	56		x	x	x
4	57	x		x	x
5	61	x			
6	62	x			
7	58	x	x	x	x

All acute lesions had some level of adherent fibrin thrombus. All chronic lesions examined, however, revealed no adherent fibrin thrombus. Goat 55 had a relatively large adherent thrombus despite the fact that there was no identifiable lesion.

Histological Examinations

The summary of lesion dimensions is presented in **Table C-4**. Diagrams and photographs from gross and histologic exams are provided in Appendix E. The analysis of the lesions was performed by Dr. Aretz, a cardiac pathologist at MGH. Two goats were ablated at a 45°C set temperature and examined acutely however, only one had lesions that could be measured microscopically. The lesion width for this goat averaged 3.1 mm with a range of 1.3-5.5 mm. The depth averaged 1.2 mm with a range of 0.2-3.1 mm. Five goats were ablated at 50°C; one examined

acutely and the others after 1-4 week survival periods. The overall average lesion width was 5.0 mm with a range of 0.3-13.3 mm. The depth averaged 2.1 mm with a range of 0.3-5.2 mm. At least 20% of the sections examined showed that the lesions were transmural (defined by the pathologist as the volume of tissue extending from the endocardial surface to the epicardial surface). Additional sections had necrosis extending into the epicardial layer of fat, many after a 4 week survival period. Continuous lesion lengths varied considerably from about 5 to 25 mm depending on whether or not all electrodes were in contact with the tissue.

Table C-4: Lesion Dimensions

Control Set Temperature: 45°C			
	Width (mm)	Depth (mm)	Length (mm)
# Sections	12	11	2
Average	3.1	1.2	10.5
Min	1.3	0.2	5.0
Max	5.5	3.1	16.0
Stdev	1.6	1.0	na (2 values)
Control Set Temperature: 50°C			
	Width (mm)	Depth (mm)	Length (mm)
# Sections	50	50	11
Average	5.0	2.1	15.0
Min	0.3	0.3	8.0
Max	13.3	5.2	25.0
Stdev	2.7	1.0	5.6

As noted grossly, the acute lesions formed using both 45°C and 50°C set temperatures showed the presence of microscopic thrombus. The tissue was thermally damaged, desiccated, and at times disrupted.

At one week, the lesions showed evidence of early organization and healing. The center of the lesions had necrotic myocytes with the peripheral myocytes being calcified. The endocardium showed no signs of disruption or the presence of thrombus.

The lesions examined after a two week survival were well healed and fibrotic. The endocardial surface of these lesions was not disrupted and did have some viable myocytes.

The tissue at three weeks was difficult to evaluate due to autolyzation but showed evidence of well healed lesions and intact endocardium.

At four weeks the lesions were very well healed with fibrotic tissue. Many of these lesions were transmural. The endocardium was intact with a thin subendocardial layer of viable myocytes in some areas.

Discussion

During the procedure, for a given position, it was common to have some electrodes with "good" electrograms (defined as relatively high amplitude, sharp deflections) and "low" pacing thresholds (defined here as less than 1.5 mA), while other electrodes had poorer values. Nevertheless, it was often the decision to apply RF energy to all or most of the electrodes. Further, because of the interest in determining if there was a correlation between RF energy delivery parameters to lesion size and location, the catheter was never repositioned with RF reapplied to the vicinity of a previous RF energy delivery site. In other words, no attempt was made to extend or connect RF burn lines, as might be expected in clinical applications. A result of this was that a lesion could not always be formed from all the electrodes selected for RF delivery as evidenced by the lesion lengths being shorter than the sum total of the electrode lengths. However, lesions that did form from multiple electrodes were fused and often transmural.

A result of choosing not to reposition the catheter is considerable variation in electrogram and pacing threshold changes. In general however, it can be seen that very significant changes in electrograms and pacing thresholds occurred for a quarter to a third of the RF applications. These changes are suggestive of lesion formation in the corresponding trajectories.

While it is likely that when an electrode has good contact it will not require more than 25W, there is no significant evidence that allowing the generator to deliver up to 50W to achieve the set temperature represents a safety concern. Maximum power delivery for Goats 54-58 was 50W. This was reduced to 25W for Goats 61 and 62. It is believed that with good contact 25W per electrode is enough power, and that more may increase the possibility of thrombus formation.

Coagulum adherent to the electrodes was occasionally observed but had little relation to the power output of the generator. It is suspected that varying degrees of contact force will affect the amount of power required to obtain a given temperature. The amount of coagulum that did form was apparently not sufficient to register a large, abrupt increase in impedance.

Acute adherent thrombus formation to a lesion is a common occurrence and is a typical response to tissue damage caused by thermal heating. Lesions examined after the animal survived for 1 week or more showed that any adherent thrombus or endocardial disruption was no longer present.

The lesions healed well over the 4 week period, often being quite fibrotic after 2 weeks. Lesions examined at 4 weeks were completely healed and still transmural. The correlation of the varying degree of viable myocytes on the endocardium to electrical conduction is difficult to make.

Further, despite the fact that lesions could not always be formed when the RF energy delivery parameters were met, the investigator did attempt to identify any apparent trends in the change of RF energy delivery parameters and lesion size/location in the animal studies, based on the available information. Only two set temperatures at 45°C and 50°C were used during the studies. Lesion size and location at four sites in the right atrium were recorded: IVC-SVC; Posterior Septum; Anterior Atrium; and IVC-TA. The following statements could be made regarding the energy delivery parameters and lesion size/location:

1. As the set temperature was increased from 45°C to 50°C, the RF power delivery appeared to increase. RF power is not a RF energy delivery parameter because in a temperature controlled system such as the Cardima's Pathfinder AFTC (Revelation Tx) system, RF energy delivery level is titrated so a set temperature is maintained and detected by the thermocouple on the catheter. The variation of RF power delivery depends on some of the known factors such as the initial set temperature, the extent of device to tissue contact and the amount of blood flow at the site. The increase in RF power delivery was more evident in the IVC-TA site where the blood flow was presumably high and heat dissipation was relatively larger (from

13.2 watts to 26.8 watts). Increase in RF power delivery was only moderate in the other sites of the atrium where blood flow was relatively lower (within 6 watts).

2. In the IVC-TA sites, as the set temperature was increased from 45°C to 50°C (RF power delivery was titrated), it appeared that bigger lesion sizes were obtained. Average lesion size per electrode used was increased from 6.5 mm^2 to 12.0 mm^2. It should be noted again that not all activated electrodes created lesions. In evaluating the lesion size, the surface area of the lesion shown on the endocardial wall was used instead of the total lesion volume. Cardima believes that the surface area of the lesion is a better representation of the lesion size than the total lesion volume because varying atrial wall thickness will affect the accuracy of volume calculation.

3. In the IVC-SVC sites, as the set temperature was increased from 45°C to 50°C, average lesion size per electrode used also appeared to increase. Lesion size per electrode used appeared to increase from 3.5 mm^2 to 5.3 mm^2.

4. Changes between the set temperature (RF power delivery) and the lesion size/location were observed in the Posterior Septum and the Anterior Atrium sites. As the set temperature was increased from 45°C to 50°C, average lesion size per electrode used was changed from 5.6 mm^2 to 4.1 mm^2 in the Posterior Septum and 11.6 mm^2 to 11.2 mm^2 in the Anterior Atrium. These changes might be representations of the true trends, however, they may be due to random changes that were not controlled in the study. Cardima believes that adequate device-to-tissue contact is an important factor in lesion formation in these sites where cardiac muscles appeared smooth and/or pectinated. As a result, the possibility of not forming lesions may be higher than other sites attempted in the study.

Conclusions

- Well healed, linearly fused transmural lesions can be created with the Pathfinder AFTC catheter system.
- Multiple lesions can be created in the atria without acute or chronic complications attributable to the Pathfinder AFTC (Revelation Tx) catheter system.
- Thrombus may form on a lesion acutely, but appears to resolve within a week.

- Coagulum may occasionally attach to electrodes as a result of RF energy delivery.
- The amount of RF power delivered varies for a given set temperature (presumably related to environmental conditions such as contact force and blood flow around the electrode and thermocouple).
- Significant electrogram reductions and pacing threshold increases after RF energy delivery are suggestive of lesion formation

CLINICAL REVIEW OF PMA

DATE: 23 JUNE 2003

SUBJECT: P020039, P020039/A1, P020039/A2 & P020039/A3

SPONSOR: CARDIMA, INC.

DEVICE: REVELATION® TX MICROCATHETER WITH NAVABLATOR ABLATION SYSTEM

Table of Contents

Section 1.0 PMA background

1.1 Indications for Use....3

1.2 Device description....3

1.3 Supportive data....4

Section 2.0 Clinical Study Background

2.1 Background....4

2.2 Summary of clinical protocol, phase III....4

2.3 Differences between phase IIB and III....6

Section 3.0 Study Results

3.1 Patient Accountability and Demographic information....7

3.2 Investigational sites....8

3.3 General procedure data....19

3.4 Ablation procedure actually performed and with what device....12

3.5 Measurement of procedural success....15

3.6 Baseline atrial fibrillation episode assessment....16

3.7 Compliance with event recording at the 6th month....17

3.8 Effectiveness of ablation procedure....17

3.9 Investigational device system effectiveness....18

3.10 Antiarrhythmic drugs (AAD)....18

3.11 Patients reported to have zero episodes at 6 months.....19

3.12 AV node ablations and surgical Maze procedures.....20

3.13 Protocol deviations.....20

3.14 Quality of life results.....21

3.15 Adverse events.....23

4.0 Conclusions.....24

5.0 Recommendations.....26

Figure 1. Patient accountability 11

Figure 2. Investigational device system evaluation.....12

Appendix.....27-62

Table 1. 30-day baseline transmission by patient.....27

Table 2. Patient Data.....30

Table 3. Listing of Study Subjects who had pacemaker implants during the course of the study.....34

Table 4. Patient with pacemaker implantation prior to the 6th month primary effectiveness endpoint assessment.....36

Table A-19 Patient tracking data.....37

Table 5. Patient identification for categories of Figure 1.....62

Section 1.0 PMA background

1.1 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 ablation catheter
- The NavAblator™, a standard 8F radiofrequency ablation catheter
- 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 electrodes and eight thermocouples in a linear array near the distal end of the catheter. The ablation electrodes are 6mm in length. Radiofrequency energy is applied to each electrode individually. The catheter is meant 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.

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. The sponsor states that "The NavAblator is intended for the creation of lesions (either linear or focal) from its tip when diverse myocardial anatomy requires the features of a "hot tip" ablation catheter to achieve effective lesions." (Volume 7, page ii)

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 has been cleared under a 510(k).

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

1.3 SUPPORTIVE DATA:

From pre-clinical studies summary (animal studies not reviewed by this reviewer):
Volume 7, page iv "the Revelation Tx was capable of creating continuous, linear transmural lesions, that a continuous lesion can be formed from sequential electrode ablations; that a set temperature of 50-55° 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."

Section 2 Clinical study background

2. 1 BACKGROUND

The study began in December 1997. It is a multi-center, prospective, non-randomized single arm study. The study was conducted in three phases with three different study endpoints and study protocols. These phases were Feasibility or phase IIa (n=10 pts), Expanded Feasibility or phase IIb (n=38 pts) and Pivotal or phase III (n=82 pts). The pivotal phase is ongoing. There were 3, 15, and 20 sites involved respectively.

The major difference between phase IIb and phase III was the addition of the NavAblator ablation catheter to the study. In many FDA correspondences and meetings with Cardima it was communicated that the use of a non-protocol device to complete the ablation procedure would be interpreted as a failure of the investigational device. Cardima had found in phase IIb that in some cases the Revelation Tx microcatheter was not effective in creating the tricuspid isthmus ablation lesion and investigators were using non-protocol ablation catheters to complete the ablation procedure. Cardima added their own 4mm ablation catheter to the investigational protocol in order to have a device system that could complete the ablation procedure.

2. 2 SUMMARY OF CLINICAL PROTOCOL, PHASE III PIVOTAL

Procedural endpoint: Electrogram amplitudes post-ablation relative to pre-ablation

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 measurement of pacing thresholds was eliminated between Phase IIb and III due to the greatly increased fluoroscopy time required.

Primary 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.

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

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 a fib 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 are allowed to rescreen. They are then required to have 9 total episodes in 90 days, which would average to be 3 per month. The re-screening period is 60 additional days.

Baseline testing: history and physical, PT/PTT & INR, "stress test", ECG and QOL questionnaires. These questionnaires are the SF-36 and the Atrial Fibrillation Severity Scale (AFSS). TEE was to be performed within 48 hours of the ablation procedure.

Procedure

During procedure all patients are heparinized with ACT maintained at 200 – 300 seconds.

Before ablation the investigator is to record bipolar electrical signals to determine good tissue contact. "In general, sharp electrograms with high frequency components and large relative amplitudes indicate good contact." Then pacing thresholds are to be measured while patient is in sinus rhythm. "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."

A pacing protocol is provided to locate the position of the phrenic nerve.

From protocol "Apply RF along three trajectories (posterolateral, posteroseptal and along the isthmus) a fourth trajectory (anterior) may be included at the option of the investigator." All three linear lesions are to be produced with the Revelation Tx. "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 protocol also states that "conduction block may be verified using coronary

sinus pacing while recording with a multipolar catheter deployed in the right atrium." And the protocol goes on to state "If bi-directional conduction block cannot be obtained with the above procedure, the physician should complete the isthmus trajectory using standard institutional procedures."

The RF energy is delivered to one of the eight electrodes at a time.

The investigator was instructed to measure bipolar electrograms and pacing thresholds "to assess changes that have occurred as a result of the RF energy application."

Follow-up

Follow-up Assessments Post Ablation

Assessment	1 month	3 month	6 month	12 month	24 month
Exam/history	X	X	X	X	
Review event recordings	X	X	X		
Review of adverse events	X	X	X	X	X
Review of prescribed medications	X	X	X	X	X
Review of hospitalizations or ER visits	X	X	X	X	
NYHA class	X	X	X	X	
ECG	X	X	X		
PT & INR	X	X			
Stress Test (masters step or treadmill)		X			
TTE		X			
Quality of Life Questionnaires		X	X		

The 24 month follow-up was by telephone.

Per investigational protocol, "Weekly event monitor transmissions are compulsory during month one, month three and month six, even if the subject does not experience symptomatic episodes."

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:

- Phase III added the NavAblator catheter to complete the linear lesion set dictated by the protocol
- 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".
- Stress test specified in phase IIb was Masters step. Phase III allowed substitution of treadmill stress.
- Holter monitor removed from the protocol between Phase IIb and Phase III.

- 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

120 patients who have undergone the linear ablation procedure of the Expanded Feasibility and Pivotal phases make up the data meant to support the market application. There is verified baseline data on 116 patients who make up the denominator for the safety analysis. 95 have completed a minimum of 6 months follow-up, were lost to follow-up or had another treatment for atrial fibrillation.

After enrollment, before ablation, the patients are monitored for 30 days and must have at least three documented symptomatic atrial fibrillation (AF) episodes within the monitoring period to be considered for the ablation procedure. There were 5 patients* whose screening rhythm strip diagnoses were disputed when reviewed by cardiologists but they had already been ablated at that point. Their data is not included in the FDA chronic effectiveness analysis but is included in the safety assessment.

The FDA used the data on the 88 patients who had unambiguous baseline episode data and either 6 month follow-up data left the study because of failure to improve or who had received another treatment for atrial fibrillation as the basis for effectiveness analysis. Table 2 in the appendix to this review shows the details for these patients as well as the baseline data on the 21 patients who had not yet reached the 6 month follow-up period. The numbers reported by the sponsor are different because they have included the 5 patients with ambiguous baseline episode results and have designated some patients as "withdrawn" when they leave the study after receiving another treatment, such as atrioventricular node ablation (AVN), for atrial fibrillation.

61 have at least 12 months follow-up and 30 have 24 months follow-up.

3/120 patients had a second ablation procedure with the Revelation Tx. Those three patients were all enrolled in Phase IIb.

Ages/sex:

89/116 male, 76.7% ages of men 27.6 to 78.3, mean was 55.7 ± 10.6 years
23/95 female, 24.2 age range of women 27.9 to 77, mean was 60 ± 11.2 years
Overall mean age 56.9 ± 10.9

72.4% of the patients had concomitant heart disease

The sinus node function of patients at baseline is not characterized.
8 patients had a pre-existing pacemaker prior to enrolling in the study.^

Ablation procedure prior to the Cardima linear ablation procedure:

Total of 33/116 patients with acute data had had a prior ablation and 22 of the 87 patients identified by the sponsor as having six month follow-up data had had a prior ablation.

Reasons for prior ablation

Atrial Flutter	15/87 (17.2%)

* IIb IIb , III III III
^ IIb III , III , III , III , III III III

30

Atrial Fibrillation	3/87 (3.4%)
SVT	2/87 (2.3%)
Atrial Tachycardia	2/87 (2.3%)

29/87 had a history of atrial flutter and 15 patients had had an ablation procedure for atrial flutter prior to the linear ablation procedure.

3. 2 INVESTIGATIONAL SITES

There were 18 sites that enrolled and performed ablation on the 120 patients included in phases IIb and III. There were 7 sites that had patients in both phases, two sites that only had patients in phase IIB and 9 sites that had patients only in phase III. Two of the 9 phase III only sites do not have any patients that have completed 6 months follow-up.

The 88-patient cohort for long term effectiveness of the device system was studied at 16 clinical sites. There are five sites with greater than 10 patients ablated and 10 sites with 5 or less.

Sites with patients in phases IIb and III

Site number	Investigational site	Ablation subjects	Included in effectiveness assessment
2	Massachusetts General Hospital	2	2
3	Johns Hopkins Hospital	6	6
4	Mayo Clinic	1*	1
5	Inova Institute for Research and Education	16	14
6	Main Line Health Heart Center	11	11
7	University of Chicago	2*	2
8	New England Heart Institute	4	4
9	Lancaster Heart Foundation	4	4
10	Diagnostic Center of CV Diseases	15	12
11	EHI-Atlantic Heart System	4⌖	3
14	Carle Heart Center	18⌖	10
15	NYU Medical Center	1⌖	1
16	Wisconsin Center for clinical Research	13⌖	10
17	Cardiac Arrhythmia Consultants	3⌖	2
18	Harper University Hospital	5⌖	3
19	Sequoia Hospital	4⌖	3
21	Access Clinical Trials	5⌖	0
23	Regional Cardiology Associates	6⌖	0

* patients in phase IIb only
⌖ patients in phase III only
Patients included in effectiveness assessment include: patients with 6 month follow-up data, patients that "withdrew" due to failure to improve, patients that "withdrew" due to AV node ablation, patients that "withdrew" because of pacemaker implantation

3.3 GENERAL PROCEDURE DATA

REVELATION® Tx Microcatheter System Catheterization and Fluoroscopy Times (minutes) (n=116-118 [a])

Total Time	min	max	median	mean ± SD
REVELATION® System Time	13	475	158	182 ± 88
Fluoroscopy Time	2	265	32	47 ± 46
Procedural time	100	755	220	250 ± 123

[a] Indicates the range of sample sizes for each of the three individual time measurements

62/111 (55.9%) procedures were performed with conscious sedation
43/111 (38.7%) procedures were performed with general anesthesia including intubation
6/111 (5.4%) procedures were performed with general anesthesia without intubation

67/118 (55.9%) procedures the patient was in sinus rhythm
34/118 (28.8%) procedures the patient was in atrial fibrillation
The sponsor reports 22 procedures in which there were catheter performance problems, 3 procedures in which there were problems with the Tx Select Switchbox, and three procedures in which there were problems with the NavAblator catheter..

Figure 1. Patient accountability

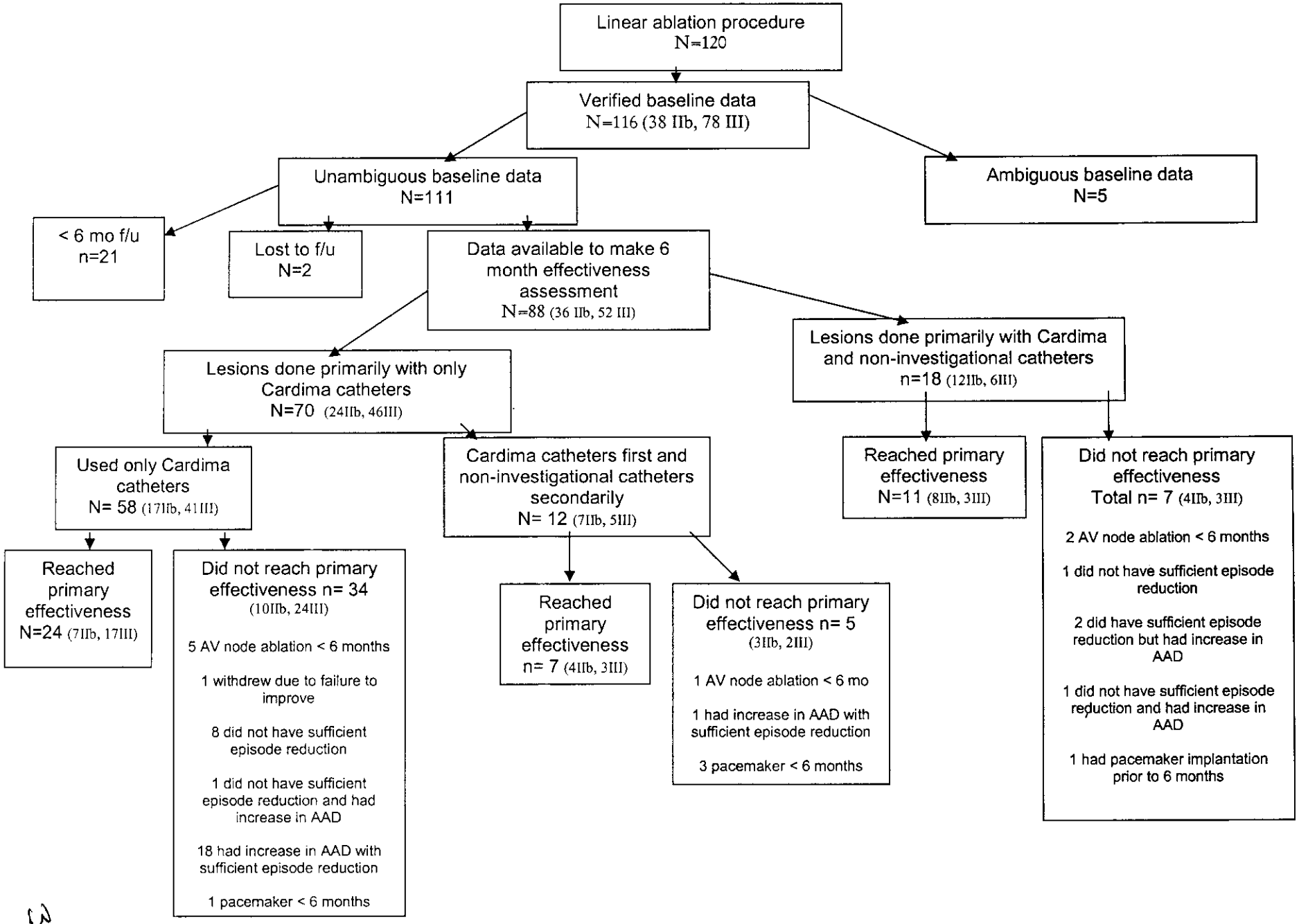
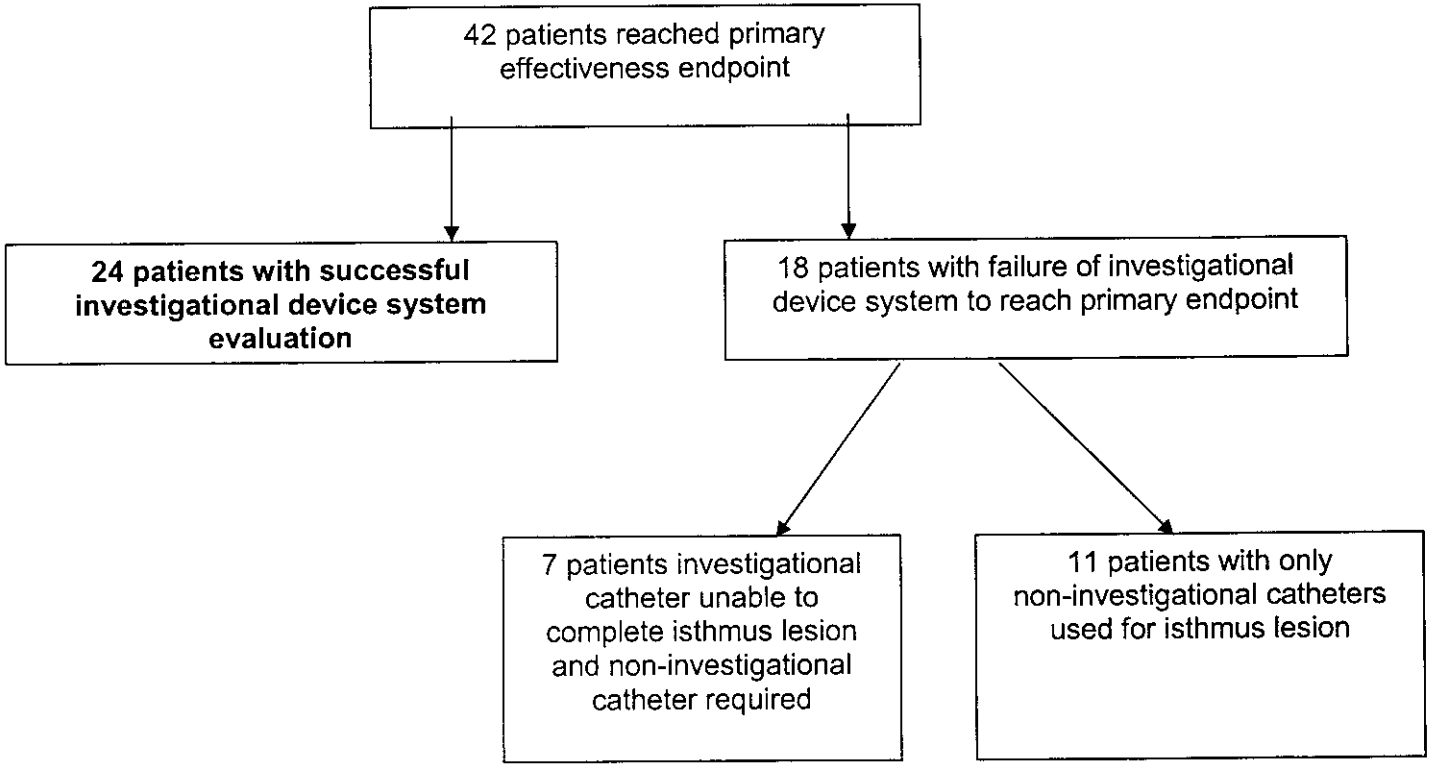


Figure 2. Investigational device system evaluation



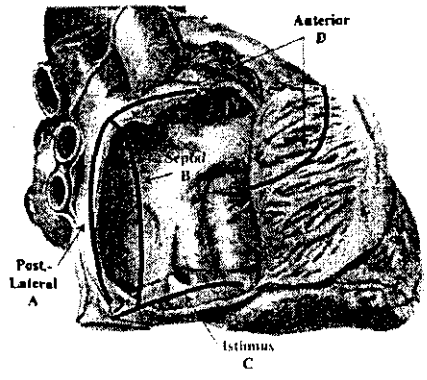
34

3. 4 ABLATION PROCEDURE ACTUALLY PERFORMED AND WITH WHAT DEVICE:

Three or four linear lesions in the right atrium were part of the ablation protocol, but not all patients received all these lesions. The locations of the lesions were: postero-lateral (A), septal (B), tricuspid isthmus (C) and anterior (D).

The study protocol directs the individual investigators to "Apply RF along three (3) trajectories (posterolateral, posteroseptal and along the isthmus) a fourth trajectory (anterior) may be included at the option of the investigator." And from the protocol "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 indication for use statement is "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."



Lesion Lines Ablated (from table 22, page 42 Cardima panel pack)

Lesion lines	Number of patients	%
ABC (standard)	95	82.6
AB	7	6.1
ACD	6	5.2
AC	2	1.7
ABCD	3	2.56
BC	1	0.8
BCD	1	10.8
Total	**115**	**100**

The Revelation Tx catheter was used to create all lesions A, B and D.

Six of the seven patients who received lesion set AB (no tricuspid isthmus lesion) had had a prior radiofrequency ablation procedure to treat atrial flutter. The result of the ablation procedure in those patients could therefore be considered to be a standard Cardima linear lesion procedure (lateral, septal, tricuspid isthmus linear lesions).

The tricuspid isthmus lesion (C) was not able to be created with the Revelation Tx in all patients. The Revelation Tx was not even attempted for the isthmus lesion in 77/108 or 71.3% of the patients who had an isthmus lesion. The NavAblator catheter was added to the study in phase III to allow a Cardima catheter to be more able to complete all the required lesions of the procedure.

The table below lists the catheters used to create the cavotricuspid isthmus lesion. The data in this table is taken from Table A-19, reproduced in the appendix to this memo, page 36. There are two rows in the table (Revelation Tx, other and NavAblator, other) that list the procedures in which the Cardima catheter failed to achieve the desired result and another ablation catheter was used (commercially available but used off label).

Catheters used to make lesion C (cavotricuspid isthmus)
(numbers derived from Table A-19)

Catheters	Number of patients (%)		
	Phase IIb n=33	Phase III n=75	Total N=108
NavAblator only	n/a	47 (62.7)	47 (43.5)
Revelation Tx only	14 (42.4)	7 (9.3)	21 (19.4)
Other only	12 (36.4)	8 (10.7)	20 (18.5)
Revelation Tx, other	7 (21.2)	1 (1.3)	8 (7.4)
NavAblator, other	n/a	10 (13.3)	10 (9.3)
Revelation Tx, NavAblator	n/a	2 (2.7)	2 (1.9)

"Other" catheters used were: Blazer (n = 18), Navistar (n = 8), Marinr (n = 6), Chilli (n = 3), and the Stinger (n = 3) for a total of 38

Successful Bi-Directional (BD) Conduction Block at Isthmus by Catheter (from Table 24, sponsor's panel pack memo page 45)

Catheters	Bidirectional block success/number tested	%
REVELATION Tx only	12/18	66.7
NavAblator only	40/46	86.9
Other only	19/19	100.0
REVELATION Tx, Other	8/10	80.0
NavAblator, Other	9/11	81.8
REVELATION Tx, NavAblator	2/2	100.0
Isthmus line not ablated	8	-
Total	89/106	83.9

Only 31/115 (27.8%) patients had the ablation procedure performed as per protocol, that is, performing the septal, lateral and tricuspid isthmus lesions with the Revelation Tx initially then moving to another catheter if the isthmus lesion was not able to be performed successfully. If the patients who had only septal and lateral linear lesions are added to this total it could be said that 39/115 (33.9%) had a per protocol ablation procedure or a standard Cardima lesion set. This number includes the patients who had a non-investigational catheter used for the tricuspid isthmus lesion.

The NavAblator catheter was exclusively used to produce a linear lesion at the tricuspid isthmus. The NavAblator was used in 59 of the 116 patients or 50.8%. It was used first or primarily in 57 patients and then in another two after the Revelation Tx had failed to produce bidirectional block. The success of the NavAblator ablation catheter in producing bidirectional block at the tricuspid isthmus was 51/59 or 86%.

The success of the non-investigational catheters was 19/19 or 100% when used alone and when used after unsuccessful use of either the Revelation Tx or the NavAblator was 17/21 or 81% in those procedures. The success of the total use of the non-investigational catheters was 36/40 or 90%. Four of the five non-investigational catheters used in this study are "standard" ablation catheters with a 4 or 5mm tip ablation electrode. One catheter, the Chilli ablation catheter, is a cooled tip ablation catheter which has been shown to produce larger ablation lesions than a "standard" ablation catheter. The Chilli catheter was used alone to produce a lesion at the tricuspid isthmus in two procedures and after a NavAblator catheter had failed to produce a satisfactory lesion in one procedure.

The non-investigational catheters were used as the only catheter to attempt an isthmus lesion in 12/33 (36.4%) of patients in Phase IIb and in 8/75 (10.7%) patients in Phase III. The latest date that a patient had an isthmus lesion created only with a non-investigational catheter (without following the protocol mandate of trying first with the Revelation Tx and then the NavAblator) was 8/14/02. There is no information in the PMA as to why physicians used non-investigational catheters for these patients without trying the investigational device as was directed by the protocol.

Cardima has provided the results of feedback from the physicians using the NavAblator, in the table below. The catheter performance was rated fair or poor by some investigators in 6/8 characteristics.

Table 20 page 38 Cardima panel pack materials
Investigator's Performance Evaluation of the NavAblator™ (*n*=63-67[a])

Characteristics	Rating (%)				
	Excellent	Very Good	Average	Fair	Poor
Ease of NavAblator™ Placement	26.9	19.4	19.4	20.9	13.4
Ease of Deflection	34.3	16.4	11.9	20.9	16.4
Stability of Placement	32.8	19.4	28.4	10.4	9.0
Stability of Deflectable tip	31.8	21.2	27.3	7.6	12.1
Radiopacity	56.1	25.8	18.2	0.0	0.0
Pacing	38.8	26.5	34.7	0.0	0.0
RF Energy Application	42.9	20.6	23.8	11.1	1.6
Overall NavAblator™ Performance	33.9	12.3	15.4	29.2	9.2

[a] Indicates the range of sample sizes for the individual characteristics rated, except for pacing, n=49.

3. 5 MEASUREMENT OF PROCEDURAL SUCCESS

The sponsor suggests that reduction of amplitude of electrograms at the lesion site of ≥50% indicates a transmural lesion.

Procedural success is discussed in section 8.7 of the sponsor's panel materials. The protocol states that "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"

Procedural success endpoints are used by the FDA in evaluating the device prior to market approval but they are also used by the individual investigator to determine when the device use has been effective and the procedure may end. In ablation procedures this would be when the physician knows that the lesion has been made effectively.

The requirement to measure pacing threshold change after ablation was removed in Phase IIb in August 1998. The sponsor discusses the difficulties in this particular measurement because of increased procedure and fluoroscopy time involved.

The discussion of acute procedural endpoints in the submission mentions that bi-directional block at the isthmus line is the success endpoint for that portion of the study. Data on measurement of bidirectional block at the cavotricuspid isthmus is provided in the table in the previous section of this review.

This study produced inconsistent data recording of amplitude reduction. The table below is excerpted from the sponsor's panel pack materials.

Table 26 page 48 Cardima panel materials
Electrogram Amplitude Reduction (n=126 procedure pairs)

Lesion Location	# Procedures	Mean Pre	Mean Post	Mean % Reduction	SD	Min*	max
Postero-septal	54	1.18	0.61	12.8%	0.73	-2.82	0.92
Postero-lateral	55	1.15	0.94	15.0%	0.71	-4.00	0.86
Isthmus	14	0.67	0.49	4.6%	0.81	-2.20	0.70
Anterior	3	0.46	0.34	35.1%	0.33	-0.02	0.58

*Minimum mean amplitude reduction

The mean % reduction does not reach the 50% goal.

Because the measurement of acute procedural success was incompletely reported 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.

The sponsor states "In conclusion, sufficient data to demonstrate either success or failure for the procedural endpoint are not available" in their section 8.7, page 48.

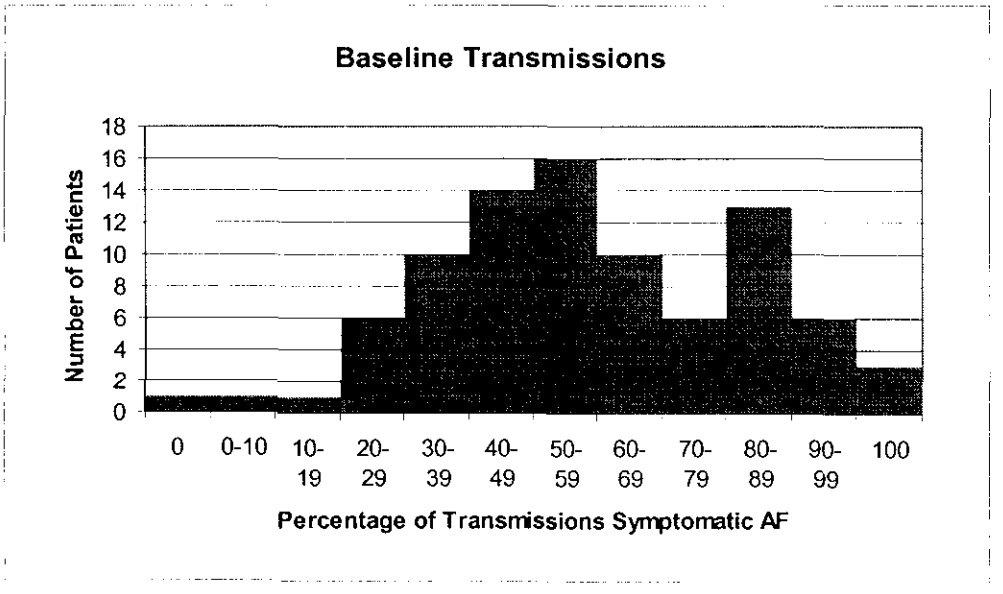
3. 6 BASELINE ATRIAL FIBRILLATION EPISODE ASSESSMENT

The patients knew that a certain number of symptomatic atrial fibrillation episodes would be required in the 30 days baseline period to be considered for radiofrequency ablation using the investigational device. They were not told the exact number required. They were given a transtelephonic monitor (TTM) and told to record whenever they had symptoms that they thought were atrial fibrillation. There were 5 patients who had the ablation procedure who had been re-screened.

Transmissions were evaluated to determine if they were actually atrial fibrillation. The percentage of actual atrial fibrillation episodes per patient ranged from 12.9 to 100%. The full results of the baseline transmissions for 87 patients are in Table 1 of the Appendix to this review. Table 1 includes the 5 patients who had ambiguous baseline data; IIB IIB III III III

Baseline number of symptomatic atrial fibrillation episodes
In 106 patients
(Patients with ambiguous baseline event numbers are excluded)

Number of episodes	Number of patients	% of total
≤ 5	41	38.7
6 -10	38	35.9
11-15	11	10.4
16-20	7	6.6
21-25	2	1.9
26-30	3	2.8
31-35	2	1.9
36-40	0	
41-45	1	0.9
46-50	1	0.9



The sponsor 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 while in other patients they recognized that they were meant to transmit once per episode.

3. 7 COMPLIANCE WITH EVENT RECORDING AT THE 6TH MONTH

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

The sponsor has submitted detailed 6th month post-procedure transmission data on 83 patients. 22 patients did not transmit any transmissions in the 6th month follow up period, which includes one of the 5 patients who had ambiguous baseline data (III 517). At least 2 patients are known to have lost the monitor or to have a non-functioning monitor. There is no explanation in the PMA submission for the reason for non compliance in the remainder of the patients who did not transmit. There also is no description of methods attempted to improve the non-compliance.

Transmissions in the 6th month post ablation

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.

3. 8 EFFECTIVENESS OF THE ABLATION PROCEDURE

42/88 (47.7%) patients reached the primary effectiveness endpoint of a % decrease in symptomatic atrial fibrillation episodes in the 6th month compared to the baseline measurement on the same antiarrhythmic regimen or reduced dosage.

The reasons for the 46 patients to have failed the primary endpoint are:

- 8 patients had an AV node ablation prior to 6 months
- 5 patients had a pacemaker implantation prior to 6 months
- 1 patient withdrew due to failure to improve
- 9 patients did not have sufficient episode reduction
- 21 patient did have episode reduction but with new antiarrhythmic medications or an increased dose
- 2 patients had both an increase in the AAD and an insufficient decrease in atrial fibrillation episodes

The sponsor presents total number of events at baseline and at 6 months in addition to the number of patients that they believe to have reached the effectiveness endpoint. The FDA does not consider it valid to group the patients together and measure change in episode frequency of the entire patient population as there is so much variability in number of episodes. The FDA has

used the protocol definition of success for determining the numbers of patients reaching the primary effectiveness endpoint.

Per section 4.2 of the protocol "Note that for the purpose of estimating the overall success rate for the six month interval, subjects electing to receive implantable pacemakers prior to the sixth month follow-up will be considered failures."

The FDA agrees with the investigational protocol classifying the patients with pacemaker implantation during the study as failures because atrial 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 measurement of the effect of the investigational device system.

The data from which the determination of whether or not the individual patient reached the primary effectiveness endpoint can be found in Tables 2 and 19 in the appendix to this review memo.

3. 9 INVESTIGATIONAL DEVICE SYSTEM EFFECTIVENESS

Of the 42 patients who successfully reached the primary effectiveness endpoint, **there were 24 patients in whom the investigational device system was a success.**

There were 18 patients that had failure of the device system to reach the primary endpoint due to 1) 7 patients in whom the investigational catheter was unable to complete the isthmus lesion and a non-protocol catheter was required to complete the ablation procedure and 2) 11 patients in whom only non-protocol catheters were used for the isthmus lesion. Details are shown in Table 2 in the appendix to this review.

Therefore, in 24/88 or 27% (18.3%, 37.1%) patients the investigational device system was effective in reaching the primary effectiveness endpoint.

3. 10 ANTIARRHYTHMIC DRUGS (AAD)

There is information on medications at six months follow up on 82 patients in the PMA. There were 22 patients on amiodarone at baseline and 18 patients at six months. Amiodarone was added to the AAD regimen of 6 patients by six months and removed in 10 patients. There were 14 patients on no AAD or only beta-blocker, calcium channel blocker or digoxin at 6 months. Of those 14 patients at baseline 6 were either on none, beta-blocker, calcium channel blocker or digoxin.

The sponsor reports 21 patients (including IIb 1004, one of the 5 patients with ambiguous baseline event numbers) who had increase in AAD from baseline to the 6th month follow up. This reviewer found one of those 21 to have a change instead of an increase in patient IIb who was taken off amiodarone and put on sotalol. Patient IIb was then considered a success of the procedure at six months but went on to have an AV node ablation at one year post ablation. This reviewer also changed patient IIb to a six month success as the increase in AAD was because of the addition of atenolol.

This reviewer found an additional 7 patients to have increases in AAD:

- IIb propafenone dose increased from 300mg/day to 600mg/day
- IIb – amiodarone added
- III amiodarone added
- III - amiodarone dosage increased
- III - amiodarone added

41

- III -- amiodarone added
- III -- amiodarone added

These 26 patients who had their AAD regimen increased are all considered failures in terms of the primary effectiveness endpoint per the investigational protocol. The patient with ambiguous baseline episode data (IIb is not included in the effectiveness results reported in this memo.

3. 11 PATIENTS REPORTED TO HAVE ZERO A FIB EPISODES AT SIX MONTHS

There were 43 patients reported to have no atrial fibrillation episodes in the 6th month post linear ablation procedure. 12 had poor compliance with the ECG transmission requirement of the protocol at six months.

Antiarrhythmic medications for the 43 patients with zero episodes reported at 6 months

MEDICATION/S	NUMBER OF PATIENTS
None (or just digoxin)	4
Propafenone, Verapamil	1
Sotalol	8
Propafenone	4
Amiodarone	7
Flecainide	5
Propafenone, atenolol	1
Flecainide, atenolol	2
Amiodarone, digoxin	1
Dofetilide	3
Dofetilide, amiodarone	1
Diltiazem	3
Metoprolol or atenolol	3

Of the total 8 patients that were on amiodarone 7 had had amiodarone added or the dose increased by the 6th month post ablation. There were 4 patients in this group who had been taken off amiodarone.

In this group is also:

- 1 patient that had a surgical Maze procedure after the 6th month
- 2 patients who had an AV node ablation, one at three months and the other 1 year post RFA
- 1 patient who had a DDDR pacer implanted at three months post RFA
- 1 patient who had implantation of an atrial defibrillator at 1.5 years post RFA

The absence of transmitted episodes at 6 months does not translate to not requiring antiarrhythmic medications or a more invasive procedure.

3. 12 AV NODE ABLATIONS AND SURGICAL MAZE PROCEDURES POST ABLATION PROCEDURE

Patients with AV node ablation post RFA

Patient	Ablation date	AV node ablation date		At or before 6 months
III	3/23/99	5/3/99	Patient requested	Yes
III	5/27/99	6/9/00	AV block started more than one year post RFA due to AAD	No
III	4/30/99	10/13/99	AV node ablation for rapid ventricular response	Yes
III	6/3/99	10/6/99	AV node ablation for rapid ventricular response	Yes
II	11/28/01	4/5/02	Pacemaker implanted prior to RFA, 1996. Had AV node ablation for persistent atrial fibrillation	Yes
III	7/16/01	11/5/01	Insurance change and therefore new physician	Yes
III	4/5/01	12/12/01	AV node ablation 8 months post RFA	No
III	7/19/01	1/3/02	Pacemaker implanted for bradycardia, AV node ablation performed prior to PPM	Yes
III	12/13/01	6/21/02	AV node ablation for worsening of CHF and AF Had sufficient episode reduction at 6 months for success	Yes
III	2/14/02	3/28/02 or 5/6/02	Persistent atrial fibrillation	Yes

11.4% (10/88) of the study patients had an AV node ablation procedure after the linear ablation procedure. 8/10 had the AV node ablation at or before the 6 month follow-up period.

Two patients had a surgical Maze procedure after having a linear ablation procedure:

- IIb – surgical Maze 14 months post RFA
- IIb – surgical Maze 6 months post RFA

3. 13 PROTOCOL DEVIATIONS

There were 56 protocol deviations identified by the sponsor which mainly consist of laboratory/assessments not performed. There were an additional 20 "Allowable Deviations". It appears that these were "allowable" because of some patient condition. But included in this list are three patient not in sinus rhythm at time of the procedure. The submission states that the patients went back into atrial fibrillation after cardioversion. These patients would not be classified as having paroxysmal atrial fibrillation if they were not able to be cardioverted. Also it is unclear how the acute procedural endpoint of these patients was determined.

The majority of patients did not have the actual ablation procedure performed as per protocol. Only 39 patients had the ablation procedure performed as per protocol, that is, performing the septal, lateral and tricuspid isthmus lesions with the Revelation Tx initially then moving to another catheter if the isthmus lesion was not able to be performed successfully.

3. 14 QUALITY OF LIFE (QOL) QUESTIONNAIRE RESULTS

Not all patients completed questionnaires both at baseline and in the 6th month and some portions of the questionnaires were not completed. There are 83 patients who have results for both baseline and the 6th month post-procedure. The results submitted by the sponsor include the QOL questionnaire data from 4 of the 8 patients who had an AV node ablation after the linear ablation procedure and before the 6th month assessment period.

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.

Baseline SF-36 scores

SF-36 scale	General US population	Study patients N=87-91*
Physical functioning	84.2 ± 23.3	71.5 ± 2.7
Role physical	80.9 ± 34	38.5 ± 4.5
Role emotional	81.3 ± 33	64.8 ±4.2
Bodily pain	75.2 ± 23.7	69.0 ±2.5
General health	71.9 ±20.3	60.7 ±2.3
Vitality	60.9 ± 20.9	44.5 ±2.3
Social functioning	83.3 ±22.7	70.7 ±2.8
Mental health	74.7 ± 18.1	73.0 ± 1.9

***5 patients did not complete the questionnaire at baseline and not all patients answered all questions**

Atrial Fibrillation Severity Scale (AFSS)

This is a disease specific quality of life scale. The sponsor 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.

From Table 36, page 63 Cardima panel pack memo
Baseline and Follow Up AFSS and Component Scores[a]

Score	Baseline (n=67-78 [e])		Six Month (n=68-79 [e])	
	Mean	SE	Mean	SE
Episode Frequency	30.2	2.1	50.4 [a]	3.0
Episode Duration	40.1	2.9	52.4[c]	4.1
Episode Severity	49.5	2.6	68.6 [a]	3.2
Total AFSS	39.6	1.6	56.4 [a]	2.5

[a] p<0.0001 by paired t-test, [b] p<0.001 by paired t-test, [c] p<0.01 by paired t-test, [d] p<0.05 by paired t-test

[e] Indicates the range of response sample sizes for each of the four domains.

Quality of life questionnaires are a relatively recent addition to clinical trials for atrial fibrillation. Gerstenfeld[1] et al has reported a single center study (copy of article follows this review memo in panel materials) in which 71 patients underwent electrophysiologic mapping and if mapping criteria were met also underwent a left atrial ablation 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.

Table 38, from Cardima panel pack memo
Six Month SF-36 and AFSS Clinically Significant Improvement
(increase by 10+ points)

Measurement Scale	Total (freq/n, (%))
SF-36	
Physical Functioning	29/76 (38.2)
Role Physical	35/80 (43.8)
Role Emotional	26/78 (33.3)
Bodily Pain	37/81 (45.7)
General Health	28/79 (35.4)
Vitality	45/80 (56.3)
Social Functioning	39/80 (48.8)
Mental Health	23/80 (28.8)
AFSS	
Episode Frequency	42/68 (61.8)
Episode Duration	27/66 (40.9)
Episode Severity	45/75 (60.0)
AFSS Total	35/64 (54.7)

Six Month SF-36 and AFSS Clinically Significant Decline
(decrease by 10+ points) by Baseline Episode Frequency (freq/n, %)

Measurement Scale	Total (freq/n, %)
SF-36	
Physical Functioning	13/69, 18.8
Role Physical	8/73, 11.0
Role Emotional	12/71, 16.9
Bodily Pain	20/74, 27.0

[1] 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

General Health	24/72, 33.3
Vitality	11/73, 15.1
Social Functioning	14/73, 19.2
Mental Health	14/73, 19.2
AFSS	
Episode Frequency	9/63, 14.3
Episode Duration	10/60, 16.7
Episode Severity	13/68, 19.1
AFSS Total	8/59, 13.6

Only in two AFSS scores, episode frequency and episode severity, and one SF-36 score, vitality, did more than half the patients improve compared to their baseline.

3. 15 ADVERSE EVENTS

There were 5 patients out of 116, or 4.3% (1.7%, 9.4%) who had definite major adverse events according to the protocol definition. In addition there were 3 patients that required implantation of permanent pacemaker shortly after the procedure, two within one or two days of the procedure and the fourth in less than two weeks of the procedure. It is very difficult to determine the influence of the procedure on the need for the pacemaker. If the 3 patients who received a pacemaker implantation shortly after the procedure are determined to be adverse events, the adverse event rate would be 8/116, or 6.9% (3.0%, 13.0%).

There were a total of 20 patients who had a pacemaker implanted during the course of the study, nine of whom also had an AV node ablation. There were 7 pacemakers implanted within 6 months of the procedure (7/88 or 8%), 5 within days of the procedure and two are identified as adverse events in the table below.

Patient	Date of procedure	Date of adverse event	Adverse event within 7 days of procedure
III [redacted] 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 [redacted] 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 [redacted] 55yo♀ 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.

46

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 a month of ablation procedure:

- Δ IIb – RFA procedure 7/6/99, pacemaker implantation 7/19/99
- Δ IIb – RFA procedure 3/22/00, pacemaker implantation 3/24/00
- Δ III – RFA procedure 12/3/01, pacemaker implanted 12/4/01 because of abnormal sinus node recovery time

Adverse event greater than one week post procedure –

- ➢ IIb – 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 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.

4.0 CONCLUSIONS

1. There were many serious problems with the design of the study.
   a. It was difficult to evaluate the safety of the device system because:
      - Single arm study with low patient numbers
      - Little characterization of sinus node function prior to ablation procedure
      - No specific adverse event ceiling pre-specified

   b. Evaluation of the effectiveness of the device system was problematic due to many factors which include:
      - New device (NavAblator) added to the protocol while the study was ongoing
      - Bias inherent in frequency of patient episode event reporting at baseline and at 6th month
        Patients knew that a certain number of events were required at baseline and were not in the 6th month
      - No method in place to determine if more than one rhythm strip was transmitted per single episode of atrial fibrillation. It was unknown if each transmission represented a discrete episode and there was data to suggest that it did not.
      - The acute procedural endpoint was unclear.

2. There were many example of poor adherence to study protocol:
   - Investigational device system was not used to create all the linear ablation lesions in 20 patients
   - The lesion set performed in the ablation procedure differed
   - The ablation procedure specified in protocol for phase IIb (Revelation Tx for all lesions, if necessary non-investigational device) followed in 26 procedures for that phase (68%)
   - The ablation procedure specified in protocol for phase III (Revelation Tx for all lesions, then NavAblator if necessary) followed in 12 procedures for that phase (15.4%)
   - Incomplete recording of acute procedural effectiveness endpoint
   - Only 36.6% of patients complied with the instructions for transmission of rhythm strips at the 6th month post-procedure.

3. A number of patients required additional procedures for atrial fibrillation after the ablation procedure.
   - 10/88 (11.4%) had AV node ablation
   - 2/88 (2.3%) had a surgical Maze procedure

4. There were many patients who required a pacemaker implantation after having the linear ablation procedure. Because the sinus node function of patients at baseline (prior to the ablation procedure) was not characterized it is difficult to determine if this rate was excessive, without a control group.
   - 5/116 (4.3%) patients acutely (4 within days of the procedure, another in less than two weeks) required a pacemaker implantation.
   - 20 total patients had implantation of a pacemaker 1 day to 1.5 years post procedure, with 9 of those patients having an AV node ablation.
   - In 88 patients included in the chronic effectiveness evaluation 20 had a pacemaker implantation (22.7%). These patients have varying durations of follow-up.

5. The major complications identified in this study were:
   - 5/116 (4.3%) (2 patients sinus node dysfunction, 1 tamponade, 1 AV fistula, 1 stroke)
   - Or 8/116 (6.9%) (as above but with 3 additional pacemaker implants)

6. Acute procedural success could not be determined in this study, as admitted by Cardima.
   - acute procedural success endpoints not consistently recorded
   - % of cases reaching acute procedural success endpoints not known
   - data of the method or indicator the individual investigator used to determine the ablation lesion or procedure was concluded was not submitted

7. There were 24/88 (27.2%) patients who reached the predetermined primary effectiveness endpoint using only the Cardima catheter system.

8. 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. Analysis of these results showed:
   - 83 patients completed at least some of QOL questionnaire at baseline and at the 6th month post procedure
   - 4/83 had an AV node ablation procedure prior to the 6th month
   - 5 patients with disputed baseline atrial fibrillation episodes are included in the 83

- more than 50% of patients had clinically significant improvement in only one SF-36 domain, Vitality
- more than 50% had clinically significant improvement in AFSS domains of Episode Frequency and Episode Severity

5.0 RECOMMENDATION

The sponsor should be sent a Not Approvable letter.

April 12, 2003

Mathematical Statistician (Heng Li, PhD) HFZ-542
Division of Biostatistics, OSB

Statistical Comments for Advisory Panel on PMA P020039; REVELATION Tx Ablation System, Cardima, Inc.

Cindy Demian, M.S. – HFZ-450
Division of Cardiovascular Devices, ODE

As one of the statisticians on the review team I would like to make a note in this review memo of some peculiarities in the current study in terms of its conduct and data analysis which have made it exceedingly difficult to extract interpretable information from the study results.

The investigational device in the current study is the Cardima® REVELATION® Tx Microcatheter with NavAblator RF Ablation System indicated for the treatment of drug refractory paroxysmal atrial fibrillation. As its name suggests, in addition to a multi-electrode ablation microcatheter (3.7F), the system consists of a single use, deflectable NavAblator™ "hot tip" ablation catheter (8F) with an electrically active tip introduced by Cardima as an optional device for ablation at the cardiac isthmus. The sponsor stated that "the introduction of the NavAblator™ makes the Cardima® REVELATION® Tx Ablation System a complete system so that non-Cardima catheter would not be required for the creation of the isthmus (flutter) line" (Panel Pack p. 43). Unfortunately, as it turned out, there have been a substantial number of the study subjects whose isthmus lines were created by "non-study" catheters. This raises the issue of how data collected on subjects not treated by the investigational device may be used to assess the safety and effectiveness of the investigational device for which regulatory approval is sought, an issue that seems to be rather unique and deserves to be thought through very carefully. However, in the current PMA submission the sponsor seems to have completely ignored this issue: the assessment of safety and effectiveness proceeded as if all the subjects had been treated by the investigational device only. The existence of a justifiable rationale underlying such an approach is hardly imaginable.

A claim is made by the sponsor that "the optional use of non-study 4mm hot-tip ablation catheters for the isthmus line occurred randomly across all phases of the study" (Panel Pack p. 43). If this claim was true, with the word 'random' being given its usual meaning in the context of clinical trials, then those patients who were treated by the investigational device following the study protocol could provide some valuable information on the investigational device. Evidential support for this claim, however, seems not to have been supplied by the sponsor. Just because the assignment mechanism is beyond the sponsor's control does not make it reasonable to conclude that it is random. It is difficult to envision the investigators randomly choosing between a "study" catheter and a "non-study" catheter, knowing that the purpose of the investigation is to seek regulatory

approval for the "study" catheter. A much more plausible assumption seems to be that the investigators selected the catheter in order to maximize the perceived benefit to the patient.

Effectiveness of the investigational device is primarily measured by percent of subjects reaching a pre-specified amount of reduction in the frequency of the spontaneous symptomatic AF episodes at the sixth month post-treatment relative to baseline. At least several factors could potentially compete with the effectiveness of the investigational device as possible partial explanations for observed reduction in the frequency of AF episodes. One of the factors has to do with selection bias. As an inclusion criterion, there must be three or more AF episodes during the 30-day baseline period. The patients who met this criterion thus include both those who typically have 3 or more episodes during a 30-day period and those who typically have fewer than 3 episodes in a 30-day period but happened to have 3 or more episodes during the 30-day baseline period. Some of the patients in the latter group would tend to have fewer episodes in a 30-day period at a later time even when the investigational device had no effect at all. Other possible factors that could lead to the observed reduction in the frequency of AF episodes include the change over time in patients' motivation to record and ability to avoid multiple recordings of a single episode. None of those possibilities haven been addressed and no steps have been taken to minimize the corresponding artifacts.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service Food and Drug Administration

MEMORANDUM

DATE: **June 23, 2003**

FROM: Cindy Demian, M.S.
Biomedical Engineer

TO: P020039
Lead Review Summary

RE: Cardima, Inc.
Revelation® Tx Microcatheter with NavAblator™ (4 mm) RF Ablation System

CONTACT: Marianne Baldwin, Vice President, Regulatory, Clinical, Quality
Cardima, Inc., 47266 Benicia Street, Fremont, California 94538 (510) 354-0166
Email: Marianne.Baldwin@cardima.com
Fax: (510) 657-4476

SUMMARY

This memo serves as the overall review memo that summar izes the review components and open issues for the Revelation® Tx Microcatheter with NavAblator™ (4 mm) RF Ablation System.

Purpose of submission

This PMA intends to show that this percutaneous catheter ablation system is safe and effective for the treatment of drug refractory paroxysmal atrial fibrillation. *Currently, there are no approved percutanoues ablation catheters that are indicated for treatment of Atrial Fibrillation regardless of rate of occurrence.*

INTENDED USE

"The Cardima® Inc., REVELATION® Tx Microcatheter Ablation System is indicated for treatment of Atrial Fibrillation in patients with drug refractory paroxysmal atrial fibrillation by mapping, pacing, and ablating with a set of continuous linear lesions in the right atrium."

Background

The PMA application and Expedited Review and was granted on November 1, 2002. This expedited review concerns **Cardima's Revelation Tx & NavAblator System** to include *two catheters*: the 6 mm Revelation Tx (3.7F) *Micro Ablation* catheter and the 4 mm NavAblator (8F) Ablation catheter. This review focused on the non-clinical aspects of the device operation and qualification. This Cardiac Ablation system requires an RF generator. However, the sponsor does not market a generator and therefore is not included in this Pre-Market Approval Application. However, the RF generator should be compatible with the catheter system. It is important to note that the RF generators used in the clinical study of the Revelation Tx/NavAblator RF ablation catheters included the Radionics RFG-3E and the IBI 1500T4, which are NOT approved marketed devices. The sponsor conducted a separate bench study to demonstrate the comparability of the performance of the two Revelation Tx ablation catheters

with the two referenced generators and the Biosense Webster Stockert 70.

DEVICE DESCRIPTION

The Revelation Tx and NavAblator Ablation system consists of the following components:

- Revelation™ Tx Micro Ablation catheter (3.7F)
- NavAblator™ 4mm Ablation Catheter (8F)

Accessories

- Naviport™ Guiding Catheter
- Revelation™ Tx Select Switch Box
- Revelation™ Tx Cables

No Generator

- RF Generator Compatibility

The Revelation™ Tx Ablation Microcatheter (3.7 F) is a single use, steerable, non-deflectable with an atraumatic distal tip coil, flexible, non-electrically active tip. It has eight electrodes and eight thermocouples temperatures sensors on the distal end of the catheter. The ablation electrodes are 6mm in length. Radiofrequency energy is applied to each electrode individually. The catheter is meant 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. This catheter is designed for the treatment of atrial fibrillation by creating linear lesions

The NavAblator™ Ablation Catheter (8F) is a single use, deflectable with an electrically active tip. It has four electrodes, including one embedded in its tip just proximal to a thermocouple. This catheter is designed to be used without a guiding catheter and has a control mechanism in the handle that activates a pull wire to steer and deflect the tip. This control mechanism "locks" the pull wire of the tip in place when the desired curve/position has been achieved.

Accessories

1) The Naviport™ Guiding Catheter
2) Tx Select Switch box
3) & Cables

Accessories to the system include the Cardima Naviport (a cleared device), the Tx Select Switchbox, and the associated connecting cables. These accessories are designed to be used with any commercially available electrocardiograph, pacing stimulator, and radio frequency generator, which have the capability of monitoring temperature from thermocouples.

The Naviport™ Guiding Catheter (offered in sizes 8F to 11F) is used to aid in the positioning of the Revelation™ Tx. The Naviport™ guiding catheter is a sterile, single use only, dual lumen (a device lumen and closed pull wire lumen) torquable, designed to support venous access to the right atrium. This exact device has already been cleared through 510(k) for the same intended use. However, it is integral

to the Revelation Tx ablation system and so is described here as an accessory to the system. The deflecting mechanism is intended to allow the guiding catheter tip to be straighten while being inserted into, removed from the heart and deflected while in the heart. The Naviport features a friction-locking mechanism that permits the distal tip to retain its deflected shape once the catheter is in position for ablation.

Tx Select Switch box

To facilitate the selection and activation of the Revelation Tx electrodes, the electrogram recorder, a pacing stimulator, or the RF generator without the need for switching cables, Cardima designed the Tx Select Switchbox. This switchbox is a passive, non-energized Class I device.

The Tx Select Switchbox allows rapid switching between electrodes receiving a pacing stimulus. The two pacing stimulator output leads may be connected to the input leads of the switchbox. Two rotary switches allow the user to select which two electrodes will receive the pacing stimulus during bipolar pacing. Alternatively, one rotary switch may be connected to a reference electrode for unipolar pacing. Recording of electrograms from the "Electrode Output" on the switchbox is possible regardless of the position of the "Active Electrode" rotary switch.

The switchbox is also designed to automatically select matched pairs of thermocouples and electrodes, so that the thermocouple just proximal to the electrode selected is activated for temperature feedback control.

RF Generator Compatibility

The Revelation Tx Microcatheter/NavAblator Cardiac Ablation system requires an RF generator, however, the sponsor does not market a generator and therefore is not included in this Pre-Market Approval Application. The RF generator parameters that determine Tx/generator compatibility are described here.

The RF generator to be used with the Revelation Tx/NavAblator Cardiac Ablation system should be compatible with ablation catheters that incorporate thermocouples for temperature feedback to the generator. In addition, the RF generator used with the Tx should have impedance sensing circuitry that will interrupt the delivery of RF energy when sensed impedance values increase beyond a pre-set limit. The RF generator should have a maximum power output limitation of 50 watts (either by factory setting or by end-user setting).

The RF generators used in the clinical study of the Revelation Tx/NavAblator RF ablation catheters included the Radionics RFG-3E and the IBI 1500T4. A separate bench study demonstrates the comparability of the performance of the two Revelation Tx ablation catheters with the two referenced generators and the Biosense Webster Stockert 70. The objective of the study was to demonstrate that any RF generator with specified minimum requirements can be used with the Revelation Tx system and the resulting lesions will be comparable to those achieved in the clinical study with the investigational generated. The results of the bench studies have been included in this module and the manufacturer states that the results demonstrate comparability of the lesions.

REVIEW TEAM MEMBERS

Cindy Demian, M.S.B.E., LEAD REVIEWER, MECHANICAL ENGINEERING & BIOCOMPATIBILITY REVIEWS
Lesley Ewing, M.D., MEDICAL OFFICER REVIEW
Heng Li, PH.D., BIOSTATISTICIAN REVIEW
James Cheng, M.S.E.E., ELECTRICAL ENGINEERING REVIEW
D. Nick Jensen, D.V.M., M.S., ANIMAL REVIEW
Lisa Kennell, STERILIZATION & PYROGENICITY REVIEW
Barbara Crowl, BIORESEARCH MONITORING REVIEW

MODULE SUBMISSIONS & STATUS

The following is a brief summary of the review history of the Revelation™ Tx Microcatheter and NavAblator Ablation Catheter System with respect to the individual modules submitted and their status, (for more details of the chronology of the file, refer to the chronology summary list):

M001 -*Biocompatibility*. Deficiencies sent September 28, 2001.

- *A001*-Sponsor responded January 28, 2002 & May 28, 2002.
- *A002*- Sponsor responded May 28, 2002.
- Accepted Module and letter sent on May 31, 2002. **Closed**.

M002 –*Animal*.

- Accepted Module and letter sent on September 28, 2002. **Closed**.

M003-*Electrical & Mechanical*

- *Electrical*- Accepted review on August 24, 2001. *Section closed.*
- *Mechanical*-Deficiencies sent March 28, 2002. Sponsor responded April 15, 2002. **Under review (rolled into PMA).**

M004-*Manufacturing & Sterility*.

- *Manufacturing-Section closed.*
- *Sterility*-**Under Review (rolled into PMA)**.

P020039 (M005) -- Phase I, II, and III clinical. **Initiated original PMA, Under review**..

In addition, three amendments to the PMA Shell were submitted: A001- update of shell plan, A002- change of contact to Ms. Marianne Baldwin, A003- July 8, 2002 meeting minutes.

MECHANICAL REVIEW---

The mechanical (Electro-Mechanical module) review was performed by the lead reviewer under M003. The following are open issues that were not adequately addressed by the sponsor:

> *In Module 3 of the PMA submission, you provided a report of lesion comparison testing which was designed to demonstrate that the NavAblator™ creates lesions that were similar in depth and degree as legally marketed ablation catheters used in the clinical study. This bench testing did*

not include ample number of legally marketed (4 mm) radiofrequency ablation catheters. As previously outlined in an email set on May 6, 2003, please provide the test results analysis from your catheter comparison testing which demonstrate the equivalence of the lesions created by the subject device and legally marketed catheters used in the clinical study.

Please address the following with respect to the Customer Experience Reports described in P020039/A002, Volume 1, pages 37-38, Volume 2, pages 81-89, Table F43:

a. *This table documents several electrical and cable failures, as well as coagulum formation. Please provide a detailed explanation of how you plan to address or mitigate these failures in order to ensure appropriate catheter performance during actual use.*

b. *This table documents several reports of the de-lamination of THV. The rationale to address this issue is insufficient because you have not provided a reasonable explanation on how you plan to ensure the manufacturability and quality assurance of your catheters. Please provide a detailed explanation of how you plan to mitigate the de-lamination of THV in order to ensure the reproducibility and manufacturability of your catheters.*

ELECTRICAL ENGINEERING REVIEW

The electrical engineering was performed by Mr. James Cheng, M.S., under the Electro-Mechanical Module 3 (M003), see attached review. The review was complete. However, there are outstanding electrical issues that were raised during the clinical review. The open issues are as follows: The clinical trial experience demonstrated possible manufacturability and quality control issues regarding the performance of the catheters. It is unclear how the sponsor will mitigate the electrical failures, coagulum, and cable failures that were observed during the clinical trial. In addition, the sponsor should clarify if these are strictly catheter design issues or primarily manufacturability issues. The sponsor will be asked the above deficiency (a) pertaining to the Customer Experiences Reports.

BIOCOMPATIBILITY REVIEW

The biocompatibility (modular) review, under M001 was performed by the lead reviewer. No outstanding issues were identified and the acceptance letter was sent May 31, 2002. The sponsor has provided documentation that they performed their studies according to Good Laboratory Practice (GLP). Since the closeout of the module, no other outstanding issues have been raised.

STERILIZATION & PYROGENICITY REVIEW

The sterilization (modular) review was performed by Ms. Lisa Kennell, see attached review under M004 for further details. Ms. Kennell indicates a major deficiency regarding failed test samples. The sponsor indicated in their reports that there were aged samples that failed tests and that tests should be repeated on samples having the corrective actions. However, no data was submitted on these samples, the sponsor will be asked the following deficiency, see below:

In Module 4 of the PMA submission, you provided incomplete documentation for in order to support a 3 year shelf life for your devices. In the report, you indicate that aged samples

failed tests and that tests should be repeated on samples having the corrective actions. However, no data were submitted on these samples. Please provide this documentation.

ANIMAL REVIEW

The animal (modular) review was performed by Nick Jensen, D.V.M., M.S., see attached memo under M002. No outstanding issues were identified and the acceptance letter was sent September 28, 2002. . The sponsor has provided documentation indicating that they did not perform their studies according to Good Laboratory Practice (GLP), where they provided reasonable justification. Since the closeout of the module, no other outstanding issues have been raised.

BIMO REVIEW

The BIMO review was performed by Barbara Crowl, see attached memo. Ms. Crowl indicated that the sponsor's inspection was cancelled on June 18, 2003. She notes that if the sponsor submits a future application, an inspection assignment can be issued at that time.

With regard to BIMO/Compliance issues, it was found that at least one of the three clinical sites inspected was unclear as to how to count/report atrial fibrillation episodes. Because a decrease in episodes from baseline to 6-month follow-up was the primary effectiveness endpoint, this may have affected the reliability of some of this data. Ms. Crowl raises valid concerns where the review team, Upper Management, as well as the Panel, are all in agreement that this file is Not Approvable. Overall, Ms. Crowl's memo indicated that the review of the data integrity at the sponsor and clinical sites showed that there were no outstanding issues.

COMPLIANCE REVIEW

The Compliance review was performed by Susan Jensen, see attached email dated June 18, 2003. Ms. Jensen indicated that Cardima was inspected from January 27, 2003 to February 3, 2003. According to Ms. Jensen the inspection was classified a Voluntary Action Indicated due to the Quality System regulation violations revealed by the sponsor. Specifically, the inspector found some deficiencies with the Quality System regulation (manufacturing) and where the firm promised to correct the deficiencies. The sponsor submitted a response to the district to correct the deficiencies and the district found their corrections were adequate. Ms. Jensen's recommendation is that concurs wit the district's recommendation of the VAI and recommend clearance for the premarket submission.

CLINICAL REVIEW

The clinical review was performed by Lesley Ewing, M.D., see attached memo.

Dr. Ewing's review recommended that the device not be approved due to a lack of a demonstration by the sponsor of the safety and effectiveness of the device for its intended use. Dr. Ewing cites the following major concerns and conclusions; refer below:

1. There were many serious problems with the design of the study.

   a. It was difficult to evaluate the safety of the device system because:
      - Single arm study with low patient numbers
      - Little characterization of sinus node function prior to ablation procedure
      - No specific adverse event ceiling pre-specified

   b. Evaluation of the effectiveness of the device system was problematic due to many factors which include:
      - New device (NavAblator) added to the protocol while the study was ongoing
      - Bias inherent in frequency of patient episode event reporting at baseline and at 6th month. Patients knew that a certain number of events were required at baseline and were not in the 6th month
      - No method in place to determine if more than one rhythm strip was transmitted per single episode of atrial fibrillation. It was unknown if each transmission represented a discrete episode and there was data to suggest that it did not.
      - The acute procedural endpoint was unclear.

2. There were many example of poor adherence to study protocol:

   - Investigational device system was not used to create all the linear ablation lesions in 20 patients
   - The lesion set performed in the ablation procedure differed
   - The ablation procedure specified in protocol for phase IIb (Revelation Tx for all lesions, if necessary non-investigational device) followed in 26 procedures for that phase (68%)
   - The ablation procedure specified in protocol for phase III (Revelation Tx for all lesions, then NavAblator if necessary) followed in 12 procedures for that phase (15.4%)
   - Incomplete recording of acute procedural effectiveness endpoint
   - Only 36.6% of patients complied with the instructions for transmission of rhythm strips at the 6th month post-procedure.

3. A number of patients required additional procedures for atrial fibrillation after the ablation procedure.
   - 10/88 (11.4%) had AV node ablation
   - 2/88 (2.3%) had a surgical Maze procedure

4. There were many patients who required a pacemaker implantation after having the linear ablation procedure. Because the sinus node function of patients at baseline (prior to the ablation procedure) was not characterized it is difficult to determine if this rate was excessive, without a control group.
   - 5/116 (4.3%) patients acutely (4 within days of the procedure, another in less than two weeks) required a pacemaker implantation.
   - 20 total patients had implantation of a pacemaker 1 day to 1.5 years post procedure, with 9 of those patients having an AV node ablation.
   - In 88 patients included in the chronic effectiveness evaluation 20 had a pacemaker implantation (22.7%). These patients have varying durations of follow-up.

5. The major complications identified in this study were:
    - 5/116 (4.3%) (2 patients sinus node dysfunction, 1 tamponade, 1 AV fistula, 1 stroke)
    - Or 8/116 (6.9%) (as above but with 3 additional pacemaker implants)

6. Acute procedural success could not be determined in this study, as admitted by Cardima.
    - acute procedural success endpoints not consistently recorded
    - % of cases reaching acute procedural success endpoints not known
    - data of the method or indicator the individual investigator used to determine the ablation lesion or procedure was concluded was not submitted

7. There were 24/88 (27.2%) patients who reached the predetermined primary effectiveness endpoint using only the Cardima catheter system.

8. 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. Analysis of these results showed:
    - 83 patients completed at least some of QOL questionnaire at baseline and at the 6th month post procedure
    - 4/83 had an AV node ablation procedure prior to the 6th month
    - 5 patients with disputed baseline atrial fibrillation episodes are included in the 83
    - more than 50% of patients had clinically significant improvement in only one SF-36 domain, Vitality
    - more than 50% had clinically significant improvement in AFSS domains of Episode Frequency and Episode Severity

Dr. Ewing cited the one major deficiency, which is located in the Deficiency Section of this memo that will be conveyed to the sponsor pertaining to the future clinical trial.

STATISTICAL REVIEW

The statistical review was performed by Heng Li, Ph.D., see attached memo.

Dr. Li's review concluded that the clinical trial design did not have well (prospectively) defined endpoints for safety and effectiveness. Based on the failure of the clinical trial to demonstrate safety and effectiveness of the catheters, Dr. Li recommended against approval of the device. Dr. Li cited the one major deficiency, which is located in the Deficiency Section of this memo that will be conveyed to the sponsor pertaining to the future statistical plan.

Brief History of the Agency's Interactions with Cardima

Cardima's clinical trial was initiated in 1997 under an approved investigational device exemption IDE G970280. The sponsor's feasibility study was approved in December 1997, where they treated 10 patients.

In July 1998, FDA Advisory Committee made recommendations for atrial fibrillation clinical study designs. In particular, they recommended a single arm study, where the patient serves as their own

control. This Advisory Committee recommended a 75 percent decrease in the frequency of symptomatic episodes or cure was considered as clinically significant endpoints in the treatment of atrial fibrillation.

In August 1998, the sponsor submitted their first progress report on their first five patients. However, there were problems with creating the isthmus line with the REVELATION Tx. The FDA recommended that Cardima could either pursue a licensing agreement with another company for use of an approved standard four millimeter ablation catheter or Cardima could design their own catheter in order to complete the procedure. Cardima opted to design their own standard four millimeter catheter. In addition, the Agency informed Cardima that the use of non-investigational device would be considered a clinical failure.

A few months later, in December 1998, the sponsor submitted their progress report from the next five patients, now a total of 10. However despite the FDA's concerns, there was still wide spread (7/10) use of non-investigational catheters in Cardima's study. Two years later in May 2000, Cardima was granted approval to begin their pivotal trial, Phase III.

In addition, the NavAblator™ 4mm catheter was added to their IDE. At that time, the Agency's thinking was that 80 patients would be treated with the new catheter and there would be sufficient acute and chronic effectiveness results within a narrow enough confidence interval to properly evaluate the NavAblator™. Again, FDA continued to communicate to the sponsor that the use of non-investigational catheters were considered failures. In June 2000, the sponsor met with the Agency where the company agreed and stated in their meeting minutes that they do not want to pool the feasibility with the pivotal. A year later in May 2001, Cardima submitted a progress report on their Phase IIb patients. FDA informed Cardima of our concerns, which were primarily based on the feasibility results. The first concern was that there was patient non-compliance with trans-telephonic monitoring. The second concern was that there was varying definitions of acute success.

PANEL REVIEW

This submission was brought before and reviewed by the Circulatory Systems Device Panel on May 29, 2003 in Gaithersburg, Maryland.

The panel voted to unanimously disapprove (7 to 0) Cardima's Revelation® Tx Microcatheter with NavAblator™ (4 mm) RF Ablation System. It is worth noting that I have highlighted the Panel's main concerns, however, for more details refer to the summary minutes and transcript.

Since the trial's inception in 1997, there is now a greater knowledge of Atrial Fibrillation as a disease. The panel discussed and raised their concerns with the design of the clinical trial. Cardima's clinical trial was based primarily on the recommendations of the July 22, 1998 (Circulatory Systems Devices) Advisory Panel, which is now somewhat outdated as technology has evolved since the 1998 Advisory Panel.

First and foremost, this clinical trial was not a randomized trial, instead the patient served as their own control and the trial did not have sufficient patient data strictly on Cardima's devices. The panel members noted that Cardima's primary investigators "contaminated the data" since they did not eliminate the use of non-investigational catheters, which in most (and not all) cases were used to create/ablate the tricuspid isthmus line since the Revelation Tx was unable to create this lesion; and the Navablator was developed for this sole purpose. The panel concurred with the FDA recommendations

specifically that the use of non investigational catheters was and should be considered as clinical failures. The panel noted this clinical trial was not a prospectively defined trial from the onset, and that the primary investigators "did not play by the rules that they designed, and furthermore, should have been eliminated from the clinical trial as primary investigators" (Dr. White). The panel also noted that missing data from the clinical trial did not translate to mean that patients did not experience episodes. Therefore, there was a lack of rigor and robust data (per Dr. Waldo, Dr. White, and Dr. Norman). In addition, the panel members concurred with the Agency's recommendation that the increase of amiodarone dosage would be considered a clinical failure. Most importantly, the panel noted in their final remarks that this was an "observational exercise" and not a true clinical trial. Since the data was improperly collected, there was no way to salvage any information from this study. It is the Agency's understanding that the sponsor would have to start again at the Pre-IDE level. Finally, the panel found very little evidence to support reasonable assurance of safety and effectiveness for the Cardima catheters (the Revelation Tx and the Navablator).

LEAD REVIEWER RECOMMENDATION

It is indisputable that the results of the clinical trail of the subject device demonstrate that the sponsor has not adequately demonstrated the safety and effectiveness of their device and that the sponsor based the design of their trial primarily on the recommendations of the July 22, 1998 (Circulatory Systems Devices) Advisory Panel. The Panel and FDA have consistently noted that the sponsor did not collect enough appropriate data to demonstrate the safety and effectiveness on the sole use of both of their investigational catheters, and that the clinical trial, in hindsight, was poorly designed. It was noted by several Panel members that this clinical trial lacked scientific rigor, i.e., there was missing data, the data was "contaminated", there was not sufficient patient data on the sole use of the investigational devices, patients were not randomized, and there were not well defined prospectively endpoints and procedures.

Based on the Panel discussions, the reviews and recommendations of the clinical and statistical reviewers, discussions with Division Management, it is my recommendation as lead reviewer and the review team that the sponsor has not demonstrated safety and efficacy of their catheter system and that the device NOT be approved (NOT APPROVABLE). It is also recommended that further clinical study of the device (both investigational catheters; specifically, the NavAblator™) is warranted based on the results of the failed clinical trial.

DEFICIENCIES

1. *We believe that the clinical evidence provided in this PMA application does not demonstrate a reasonable assurance of safety or effectiveness as described in 21 CFR 860.7(d)(1) and (2), respectively. Specifically, we note the following issues which need to be addressed with respect to the submission and analysis of clinical data submitted in this application:*

    a. *The clinical study lacked an accurate measurement of effectiveness endpoints, due to the following confounding factors:*

        i. *Failure to assure compliance with the measuring tool used to collect data to evaluate the effectiveness endpoint; and*

ii. *Failure to clearly define a method to determine if symptomatic episodes reported by the patient represented discrete episodes of atrial fibrillation.*

b. *The clinical study lacked a consistently defined acute procedural endpoint that would allow assessment of effectiveness of the device system and provide a basis for developing instructions for use.*

c. *The clinical study lacked complete adherence to the investigational protocol by all investigators at all investigational sites, with respect to:*

i. *performance of the same ablation procedure with the investigational device; and*

ii. *initial attempted use of the investigational device system catheters only.*

d. *The clinical study results were potentially biased by changes to patient antiarrhythmic medications.*

e. *The clinical study did not contain careful characterization of the study population in terms of the pre-existing co-morbidities, such as sinus node function, which made it difficult to evaluate the effects of the ablation procedure on key patient parameters.*

f. *The lack of a control arm made the trial vulnerable to biases and artifacts, such as placebo effects.*

We recommend that you schedule a meeting with us to discuss how these issues will be addressed in a future submission.

2. *In Module 3 of the PMA submission, you provided a report of lesion comparison testing which was designed to demonstrate that the NavAblator™ creates lesions that were similar in depth and degree as legally marketed ablation catheters used in the clinical study. This bench testing did not include ample number of legally marketed (4 mm) radiofrequency ablation catheters. As previously outlined in an email set on May 6, 2003, please provide the test results analysis from your catheter comparison testing which demonstrate the equivalence of the lesions created by the subject device and legally marketed catheters used in the clinical study.*

3. *Please address the following with respect to the Customer Experience Reports described in P020039/A002, Volume 1, pages 37-38, Volume 2, pages 81-89, Table F43:*

a. *This table documents several electrical and cable failures, as well as coagulum formation. Please provide a detailed explanation of how you plan to address or mitigate these failures in order to ensure appropriate catheter performance during actual use.*

b. *This table documents several reports of the de-lamination of THV. The rationale to address this issue is insufficient because you have not provided a reasonable explanation on how you plan to ensure the manufacturability and quality assurance of your catheters. Please provide a detailed explanation of how you plan to mitigate the de-lamination of THV in order to ensure the reproducibility and manufacturability of your catheters.*

4. *In Module 4 of the PMA submission, you provided incomplete documentation in order to support a 3 year shelf life for your devices. In the report, you indicate that aged samples failed tests and that tests should be repeated on samples having the corrective actions. However, no data were submitted on these samples. Please provide this documentation.*

REVIEW TEAM RECOMMENDATION

NOT APPROVABLE

1. *The PMA submission requests approval for two different ablation catheters, the Revelation Tx and NavAblator. In your supporting clinical trial, the Revelation Tx was tested in 95 patients and you provided 6 month follow-up on 79 of those patients. The NavAblator was tested in 41 patients, five of which required a non-investigational ablation catheter from another manufacturer to complete the procedure. FDA is concerned that the amount of clinical evidence provided for the NavAblator may not provide a reasonable assurance of safety and effectiveness for this device. Please provide additional clinical evidence on the NavAblator or, alternatively, justify why the amount of testing already provided provides a reasonable assurance of safety and effectiveness.*

Cardima's PMA submission requests approval for a system to treat atrial fibrillation. The system originally comprised the REVELATION® Tx Microcatheter and a 4mm "conventional"[1] RF ablation catheter considered "standard institutional procedure" for creating RF lesions at the isthmus of the right atrium. Later, Cardima introduced its own 4mm RF ablation catheter, the NavAblator.

The protocol required the use of the REVELATION Tx for the septal and lateral lesions and, for the isthmus line, investigators were requested to first attempt the lesion with the REVELATION Tx, then, if the anatomy of the isthmus varied or was too bulky, a "conventional" catheter could be used. After the introduction of the NavAblator, the "conventional" ablation catheter became a third option after attempting with the Revelation Tx and the NavAblator, if bi-directional block still could not be confirmed. The device use for creation of the isthmus line in this study reflects this practice.

In response to FDA's concern that the amount of clinical evidence provided for the NavAblator may not provide a reasonable assurance of safety and effectiveness for this device, Cardima is herewith presenting additional clinical evidence supporting the rationale that the data reported herein provide reasonable assurance of safety and effectiveness for the REVELATION Tx and NavAblator Ablation System for the treatment of AF.

The Original PMA submission reported that NavAblator was tested in 41 patients, five of which required a non-investigational catheter from another manufacturer to complete the procedure. That report was based upon data as of July 31, 2002. Table A-1, below presents an additional 18 patients for a total of 59 patients in whom the NavAblator has been tested including 12 who also required a non-investigational catheter to complete the procedure.

[1] "Conventional" in this context means approved "hot tip" RF ablation catheter.

Table A-1
Isthmus Lesion Creation by Device by Availability (Study Phase)

Ablation Device	Phase IIb (n=38) (Isthmus Lesion n=33)	Phase III (n=77) (Isthmus Lesion n=75)	Total (n=115*) (Isthmus Lesion n=108)
REVELATION Tx Only	14/33 (42.4%)	7/75 (9.3%)	21/108 (19.4%)
REVELATION Tx w/Other	7/33 (21.2%)	1/75 (1.3%)2	8/108 (7.4%)
NavAblator Only	-	45/75 (60.0%)	45/75 (60.0%)
NavAblator w/REVELATION	-	2/75 (2.7%)	2/75 (2.7%)
NavAblator w/Other	-	12/75 (16%)	12/75 (16%)
Total NavAblator Experience		59/75 (78.6%)	59/75 (78.6%)
Other only	12/33 (33.3%)	8/75 (10.6%)	20/108 (17.6%)

*Data pending at the site for one subject

The data summarized above reflects the use of the investigational devices exclusively in approximately 80% of the isthmus lesions created, adjusted for the availability of the NavAblator.

However, it is important to recognize that the isthmus lesion is but one of three or four lesions used for the treatment for atrial fibrillation. The treatment outcomes at the six-month follow up interval for the treated patients by isthmus lesion device is illustrated in Table A-2.

Table A-2
Treatment Outcome Results[1] at Six Months Relative to Baseline by Device Employed to Create the Lesion at the Isthmus Line

Outcome	NavAblator[3] (n=28)	REVELATION Tx (n=17)	Other (n=28)	Total (n=73)
Treatment Success[2]	21/28 (75.0)	16/17 (94.1)	26/28 (92.9)	63/73 (86.3)
Episode Reduction[4]	6.0 ± 10.8	8.6 ± 6.1	10.0 ± 10.6	8.2 ± 9.8

1 These results do not include 8 subjects who did not have the isthmus line ablated and 5 subjects whose baseline episode frequency was ambiguous

2 Patient treatment success, 50+% reduction in episodes, freq/n, %

3 Includes 2 subjects whose isthmus line was treated with both REVELATION Tx and NavAblator.

4 mean ± SD

These results illustrate that the criterion for treatment success was exceeded in all groups.

It is important to recognize that these data reflect the outcome of the entire procedure, including the complete lesion set, the procedure duration, skill of the investigator,

4

method of sedation, pre-existing and concomitant conditions of the study subjects, among others. The isthmus catheter used is not the only variable affecting treatment success and may not affect the treatment outcome at all.

It is also important to recognize that creating a linear lesion at the isthmus line is a challenging task, given the irregularity of the anatomy in that region of the atrium. The use of either the NavAblator or another "conventional" ablation catheter means that there has already been a prior attempt with the REVELATION Tx or an assessment of the isthmus anatomy to determine the probability of success with the Tx. In Phase III, the use of another ablation catheter means that both the Tx and the NavAblator had been tried or assessed for likely success in the presenting anatomy.

The successful achievement of bi-directional block depends upon the combined effects of investigator skill and isthmus anatomy and, in some cases, it is not achieved during the procedure at all, regardless of the type or number of catheter(s) used.

In conclusion, Cardima believes that the accumulated evidence presented here is sufficient to provide reasonable assurance of safety and effectiveness of the REVELATION Tx Ablation System, including the NavAblator or a 4mm conventional[1] RF ablation catheter in creating endocardial lesions in the right atrium for the treatment of atrial fibrillation.

2. *You provided summaries of the follow-up and outcome for the patients involved in the clinical trial. Additional information is needed in order for FDA to thoroughly review your application. Please provide a table of all patients who have been treated with your ablation system. The columns should include the patient identifier, date of procedure, identify and number of catheters used, follow-up completed and dates, number of atrial fibrillation episodes at baseline, number of atrial fibrillation episodes at 6 months, medications at baseline, and medications at the 6 month assessment.*

   A summary of all patients who have been treated with Cardima's ablation system is presented in the requested format in Table A-19, Appendix A-1, Volume 1. As requested, this summary includes the patient identifier, date of procedure, identity and number of catheters used, follow-up completed and dates, number of atrial fibrillation episodes at baseline, number of atrial fibrillation episodes at 6 months, medications at baseline, and medications at the 6-month assessment.

3. *You provided a summary of patient atrial fibrillation episode reduction in terms of number of patients who had certain frequencies of events at six months. Please provide a complete tracking of the change in event frequency per patient or patient group. For example, for the group of 14 patients who had 3 events per month at baseline, please identify the status of these 14 patients at the 6 month follow-up. This data presentation necessitates the removal of the 5 patients who did not have an accurate baseline frequency recorded. In addition, please provide the patient identifiers of those 5 patients.*

A complete tracking of the change in event frequency per patient by baseline episode is provided in Table A-4. The five patients whose baseline frequency was ambiguous [redacted] ave been removed from this table. Where no data are listed, either the subject has not yet reached the specific interval or the data have not yet been verified for entry. This listing is also presented by patient in Table A-20, Appendix A-1.

Table A-4 – Status of Subjects by Baseline Episode Frequency

Phase	Pt ID	Baseline Episodes	3-Month Episodes	6-Month Episodes	Episode Group*
IIB		3	0	0	a
III		3	2	0	a
III		3	0	3	a
III		3	9	1	a
III		3	0	0	a
III		3	1	0	a
III		3	0	0	a
III		3	4	0	a
III		3	6		a
III		3	1		a
III		3	0		a
III		3	2	0	a
III		3	0	0	a
III		3			a
IIB		4	5	0	a
IIB		4	0	0	a
IIB		4	0	0	a
IIB		4	0	0	a
IIB		4	0	0	a
IIB		4	0	1	a
IIB		4	2		a

6

Table A-4 – Status of Subjects by Baseline Episode Frequency

Phase	Pt ID	Baseline Episodes	3-Month Episodes	6-Month Episodes	Episode Group*
III		4	5	1	a
III		4	0	1	a
III		4	2	1	a
III		4	0	0	a
III		4	0	0	a
III		4	4		a
III		4	1	2	a
III		4	0	0	a
IIB		5	0	13	b
IIB		5	5	1	b
III		5	0	6	b
III		5	1	0	b
III		5	2	0	b
III		5			b
III		5	8	0	b
III		5	0		b
III		5	4	7	b
IIB		6	4	2	b
IIB		6	0	3	b
III		6	9	4	b
III		6	0	0	b
III		6	7	2	b
III		6	0	3	b
III		6	0	0	b
III		6	0	0	b
III		6	1		b
III		6	7		b
III		6			b
III		7	1	0	b
III		7	0	0	b
III		7	4	7	b
III		7	9		b
III		7	4	2	b
IIB		8	5	1	b
IIB		8	5	2	b
III		8	2	4	b

7

Table A-4 – Status of Subjects by Baseline Episode Frequency

Phase	Pt ID	Baseline Episodes	3-Month Episodes	6-Month Episodes	Episode Group*
III		8	3	3	b
III		8	0	0	b
III		8	20	13	b
III		8			b
III		8			b
IIB		9	1	0	b
IIB		9	1	0	b
IIB		9	0	0	b
IIB		9	0	3	b
III		9			b
III		9			b
III		9			b
III		9	2	10	b
III		9	2		b
III		9	0	0	b
IIB		10	1	4	c
IIB		10	23	0	c
III		10	0	3	c
III		10	0		c
III		10			c
III		10			c
III		10	30		c
IIB		11	7	8	c
IIB		11			c
IIB		11	1	2	c
IIB		12	3	1	c
IIB		12	8	7	c
IIB		12	11	4	c
IIB		13	6	0	c
IIB		13	8		c
III		13			c
IIB		14	7	1	c
IIB		14	4	0	c
III		14		4	c
III		15	5	4	c
III		15			c

8

Table A-4 – Status of Subjects by Baseline Episode Frequency

Phase	Pt ID	Baseline Episodes	3-Month Episodes	6-Month Episodes	Episode Group*
III		16			c
III		16	0		c
IIB		17	14		c
IIB		19	1	0	c
III		19	5	1	c
III		19			c
III		19	0	2	c
IIB		20			d
III		22	4	2	d
III		25			d
III		26	0	3	d
III		26			d
IIB		29	13	7	d
III		31	30	1	d
IIB		32	1	1	d
III		40			d
III		51	15	1	d
IIB		52	6	0	d

* Group a: 3-4 episodes, group b: 5-9 episodes, group c: 10-19 episodes, group d: 20+ episodes

4. *You provided summary adverse event information for your clinical trial. Please provide additional adverse event information on patients [redacted] Specifically, provide a summary of the adverse events that occurred and provide all the data monitoring forms and any other information, such as discharge summaries, used for your assessment of these adverse events.*

Adverse event information for this clinical trial was reported and assessed by the sites according to definitions provided by the protocol. AEs that were determined to be Major Complications were further assessed by Cardima to assure compliance with the FDA definition. When information provided by the sites was not sufficiently clear, source documents from medical records such as operative reports, lab reports, office visit notes, or a letter from the investigator were used to clarify and confirm the nature of the event.

Those complications that clearly met the criteria for "Major" were so classified. Those that did not, but still occurred within the first week following the procedure and were significant, but did not require major intervention to resolve (e.g., adjustment of an anti-arrhythmic drug to resolve 2.4 second pauses) would not be classified as a "Major Complications".

If the site believed an event to be an adverse event, it was reported as such. However, if the AE was reported to be a "Major Complication and Cardima's assessment of the event consistent with the definition of Major Complications presented in CDRH Guidance document "Recommended Clinical Study Design for Ventricular Tachycardia Ablation" dated May 7, 1999 differed, the event was not treated as a "Major Complication" in the data analysis.

All data monitoring forms for the specified patients, including supporting documents used to assess the adverse events are included in Appendix 3, Volumes 3, 4, 5, and 6.

Table A-5, below, presents the requested summary of the adverse events reported for the specified study subjects. An updated listings of adverse events for all study subjects is included in the updated clinical data presented in Appendix A-3, Volume 2.

Table A-5 - Adverse Event Summaries for Twelve Study Subjects

Subj. ID	Procedure Date	AE Onset Date	AE Description and Outcome
IIb	06/09/99	06/12/99; 06/27/99	This patient entered the study with sinus bradycardia and some non-significant structural heart disease (LV hypertrophy). The site reported two (2) AEs for this subject. The first event was a sore throat and upper respiratory infection with "mild" symptoms noted prior to discharge. This event was determined by the investigator to be "probably" related to the procedure. This event was noted to have resolved on June 14th. However, on June 27th, the subject presented with possible pneumonia and a UTI with symptoms noted to be of "moderate" severity. The complication was reported resolved on 6/29/99. The investigator was uncertain if this event was related to the procedure. Subject continued through the 24 month F/U without further AEs.
IIb	07/08/99	07/09/99	This patient entered the study with Atrial Flutter, despite two prior RFA procedures for this arrhythmia in August and September of 1997. One AE was reported for this study subject at discharge consisting of a UTI with mild symptom severity and a reported start date of 07/09/99 and a resolve date of 07/11/99 following Rx therapy. The investigator considered this event to be probably related the procedure, not to the device. Subject continued through the 12 month F/U interval and then had a surgical MAZE procedure for recurrent AF and withdrew from the study.
III	02/21/01	516/01	This patient entered the study with Atrial Flutter, despite a prior RFA procedure for this arrhythmia on 09/08/00. One AE was reported for this subject with complaints of dizziness (syncope) "moderate" in severity and an onset date of 02/28/01. This was initially reported by the site as SA Block in error. Electrogram strips recorded by the cardiac event monitor on 02/28/01 documented 2.4 second pauses. A reduction in the AAD dosage resolved the event. The investigator believed this event to have a probable relationship to the procedure, not to the device. The subject continued in the study through the 12 month F/U without further AEs and is still continuing.
III	06/08/01	07/09/01	This patient enrolled in the study with no significant history of anything but AF. Following treatment under this protocol, subject was discharged in NSR, but back in AF on 6/12/01. A series of attempts at cardioversion were performed beginning with successful medical

Subj. ID	Procedure Date	AE Onset Date	AE Description and Outcome
			cardioversion (Rhythmol) on 6/26, return to AF on 6/29/01 that was unsuccessfully treated with an increase in Rhythmol. On 7/9/01 mechanical cardioversion was successful, following an admission for same on 7/6/01 that was abandoned due to elevated INR (10.7). This patient was also admitted to the hospital ER on 7/19/01 with chest pain and an EP study revealed Atrial Flutter with variable heart block. This was reflected on the patient's 3-month follow up Arrhythmia Event CRF. This subject completed the 12-month FU interval without further events.
III	5/30/01	5/31/01	This patient entered the study with a history of intermittent hypertension, "seasonal asthma", and hyperlipidemia but with an otherwise normal medical history. A report of pericarditis was documented for this subject prior to discharge. No other AEs were reported for this subject, but he was admitted to the ER on 10/08/01 for a successful medical cardioversion following a prolonged episode of AF beginning 9/25/01. The subject did report symptoms noted on 7/25/01, 9/18/01, and 9/24/01 that could not be transmitted due to heart card battery failure. The subject continued in the study with no further symptoms and no further AEs through the 12 month assessment on 5/11/02.
IIb	04/14/99	04/15/02	This patient was enrolled in the study with a history of mild asthma, AF, and previous EP study, no ablation. The patients weight is 290.5 lbs. On 04/15/99 the patient complained of not being able to take a deep breath and numbness to right thigh. No SOB, CP, EKG normal, echo, normal, and CXR normal. This was reported as resolved on 04/29/99. On 7/23/99 the AE resolved. No sensory loss or motor loss. Patient has continued follow up visits and completed the study after 24 months on 03/14/02.
III	10/21/99	10/21/99	This patient enrolled in the study with history of AF and A flutter. After the procedure a hematoma to the right groin was seen after femoral lines were pulled out. An ULS was performed showing no pseudoaneurysm. It was determined that this was related to the procedure but not to the study device. The severity was listed as moderate. It was still present on 10/27/99, 11/18/99 and resolved 1/24/2000. Patient was receiving Coumadin at baseline, INR within range before procedure and post procedure patient was again placed on Coumadin through month 12. The patient completed follow up without further events and completed the study after 24

Subj. ID	Procedure Date	AE Onset Date	AE Description and Outcome
			months on 1/23/02.
III	4/05/01	04/06/01	This patient entered the study with a history of hypertension, anxiety and depression, and cholelithisasis with a cholecystectomy, as well as AF. The baseline EKG revealed "marked sinus bradycardia" and the baseline TEE revealed evidence of a very small, L to R shunt, but bubble study showed no evidence of R to L shunting and there was no evidence of thrombus in the LA or LAA, so it was not considered exclusionary. The subject's pre-discharge EKG showed sinus bradycardia (04/06/01) and reports on the same date were made for right groin bleeding and back pain, pain and skin irritation of the coccyx.
		4/11/01	The right groin incision was cultured with staph., and reported resolved on 4/22 after course of Levaquin.
		4/14/01	The subject reported palpitations and was diagnosed with SVT that resolved on 4/16/01.
		5/07/01	At the one-month visit (05/07/01), the EKG revealed sinus brady and complaints of severe symptoms of chest pain, SOB, lightheadedness, fatigue and anxiety where the severity for these symptoms at baseline were minimal.
		6/11/01	Subject complained of increased lightheadedness.
		7/09/01	At the three month visit, subject reported chest pain during the stress test but had a normal EKG where there was sinus brady at post procedure discharge.
		8/25/01	Worsened fatigue
		8/26/01	Chest and abdominal pain that resolved on 9/01/01
		8/31/01	Worsened hypertension
		8/31/01	Sore throat that resolved on 9/07
		9/05/01	Cough that resolved on 9/07
		9/04/01	Chest and Abdominal pain that resulted in hospitalization for perfusion scan and CXR.
		9/17/01	Upper respiratory Infection that resolved on 9/24/01
		9/18/01	Rhus dermatitis and headache. Dermatitis resolved on 11/26/01.
		9/20/01	At what was treated as the 6 month visit, subject was reported to be in sinus brady with an EF of 30% and a slight decrease in the severity of symptoms for chest pain, SOB, lightheadedness, fatigue and anxiety.
		10/22/01	Viral cold
		11/15/01	Anxiety

Subj. ID	Procedure Date	AE Onset Date	AE Description and Outcome
		12/10/01	Cardioversion (hospitalized) that was unsuccessful
		12/12/01	Eight months after Cardima RFA, subjects had AVN ablation and PPM.
III	7/19/01	7/19/0)	This patient entered the study with a history of sinus bradycardia, atrial tachycardia, intermittent lightheadedness and dizziness and atrial flutter. As is the practice with this site, any report of a health change was recorded as an adverse event, resulting in a report of a pre-procedure AE of "worsened lightheadedness". The first post procedure event was an arrhythmia of moderate severity that was reported to have occurred during the procedure. This event was determined by the investigator to have been not related to the study procedure.
		7/20/01	The day following the procedure, the subject reported three additional AEs of increased lightheadedness, a swelling right hand and generalized discomfort. This was reportedly resolved the same day. All of these AEs were determined by the investigator to be not related to the device, the latter two to be possibly related to the procedure and the increased lightheadedness to be unrelated to the procedure
		8/11/01	The subject reported a headache of moderate severity unrelated to either the device or the procedure.
		8/20/01	At the one-month follow up visit, this subject was shown to have sinus brady during the scheduled EKG. This was also reported as an AE of sinus bradycardia along with chest pain of moderate severity and determined by the investigator to be unrelated to either the device or the procedure. The chest pain was reported to have resolved the following day (8/21/01).
		8/22/01	Additional AEs were reported with an onset date of 8/22/01 of endolymphatic hydrops of moderate severity and sinus bradycardia. The former (hydrops) was reportedly resolved on 8/29/01 and determined by the investigator to be unrelated to either the device of the study procedure.
		9/03/01	Two more AEs were reported with start dates of 9/03/01 that were difficulty sleeping and fatigue, both of minor severity and unrelated to device or procedure.

Subj. ID	Procedure Date	AE Onset Date	AE Description and Outcome
		10/24/01	At the 3 month interval, the subject again produced an EKG with sinus bradycardia. On 11/12/01 the subject was admitted with AF for a scheduled cardioversion with amiodarone, followed on 11/14/01 by a report of a "sensation of moving in slow motion" that resolved on 11/20/01.
		1/3/02	On the subject had an AV node ablation and a pacemaker implant. This date is considered to be within the defined window for the 6 month assessment (6 months+/-4 weeks), so the patient was not considered a treatment failure. In addition, the pre-existing bradycardia suggest this subject had a pre-existing condition that led to the pacemaker treatment. Further AEs following the pacemaker implantation and associated with that procedure were reported that ranged from clostridium difficile and intermittent stomach pain to continuing endolymphatic hydrops. This subject is continuing to participate in the study.
III	12/13/01	12/13/01, 03/11/02	This patient entered the study with a dual chamber pacemaker implanted and a history of CAD (NYHA Class II on 11/05/01), PTCA, MI, a moderately dilated LA (4.9-5.0cm) with moderate LV hypertrophy, hypothyroidism, and a cancerous tumor on the right arm. Prior to discharge AEs were reported of AF and defibrillator burns from the procedure. No AEs were reported at the 1 month visit, but the patient's 1-month EKG showed AF. At three months, a report of increased CHF with an NYHA Class III was recorded. The investigator determined that this event was due to pre-existing CHF and not the procedure or the device. The three-month echo showed a modest decrease in atrial dilatation, recorded as mild rather than moderate. The subject completed the 6 month follow up and is continuing in the study.
III	02/14/02	02/14/02	This patient enrolled in the study with a history of AF, chest pain, mitral regurgitation, mild LV hypertrophy, headaches since childhood, sciatica, and CAD. The patient experienced back pain at the end of the procedure which was not device related, possibly related to the procedure and moderate in severity which resolved 02/15/02. On 02/15/02 the patient complained of sore throat and difficulty sleeping both considered not related to the device or the procedure. On 02/19/02 the patient was reported to have a right groin hematoma that was not related to the device but considered related to the procedure. This resolved on 03/08/02. Patient was

15

Subj. ID	Procedure Date	AE Onset Date	AE Description and Outcome
			placed on Coumadin prior to discharge. The patient developed a new onset of A Flutter that was seen on the weekly transmissions on 03/11/02 and hypertension at the one month visit. On 03/21/02 the patient developed persistent AF and had an AVN and a permanent pacemaker implanted on 03/28/02.
III	04/27/01	04/28/01	This patient entered the study with a history of hypertensive heart disease and a prior RFA for atrial fibrillation three years earlier. One major complication was reported for this study subject that was determined by the investigator to be related to the procedure. The complication was an AV fistula reported prior to discharge that was successfully surgically repaired on 05/04/01 and patient was discharged home on 05/07/01. No further problems associated with this event were reported. However, in July, 2001 this study subject did report a change in breathing pattern, a non-productive cough and numbness in right thigh (at the incision site of the AV fistula repair). These were all reported to be mild in severity and, except for the incision numbness, not related to the investigational procedure. The Incision numbness was reportedly resolved on 7/19/01 and the cough and breathing pattern change were reported to be resolved on 09/21/01. At the 6-month (10/23/01) and 12-month (03/12/02) intervals, the patient reported chest pressure and shortness of breath that the investigator determined to be not related to the study procedure (but likely due to the subject's pre-existing hypertension). These symptoms were reported to be mild in severity and had not resolved at the last assessment interval. The subject continue study participation.

5. *You provided summary data for all patients treated with your ablation system, including patients who were treated with non-investigational ablation devices, such as a cooled ablation catheter. Please provide clinical and statistical justification for pooling these data. Your justification should include the effectiveness data assessment for the patients treated only with the investigational device and comparison with the group treated with both the investigational device system and other devices. Please explain why the patients who required treatment with a non-investigational device should not be treated as device failures.*

The clinical justification for pooling these data includes recognition that the conventional RF ablation catheters perform similarly in the creation of endocardial

RF lesions and Cardima has demonstrated that the lesions created with the NavAblator are similar to other 4mm RF ablation catheters (see M010005/M003, Appendix II, page 368).

In addition, the approved protocol was designed to investigate an ablation system that was to be used to create a set of lesions in the right atrium to treat atrial fibrillation. That system comprised the REVELATION Tx microcatheter, a guiding sheath (that has since been cleared under a 510(k), and, if necessary to complete the isthmus lesion, a "conventional" RF ablation catheter. Because creating a linear lesion at the isthmus line is a challenging task, given the irregular anatomy in that region of the atrium, it was expected that there may be a small number of patients whose anatomy would require an additional effort to achieve bi-directional block at the isthmus and the approved protocol provided for and permitted this additional effort (with a conventional RF ablation catheter.

Table A-6 illustrates similar complication rates among those patients treated with the NavAblator and conventional RF ablation catheters and those who were treated entirely with the REVELATION Tx. In addition, Table A-7 illustrates similar outcomes in treatment success and episode reduction as well as baseline to six months changes in quality of life. Therefore, Cardima believes these clinical and statistical results are evidence that pooling the data for these devices is reasonable and justified.

Clinical complications by device used to create the isthmus line are presented in Table A-6. Only acute complications are presented here because other, non-device related variables affect clinical outcomes beyond the peri-procedure period.

The statistical and effectiveness assessments are presented in Table A-7.

Table A-6 -Complications by Device used to Create Isthmus

Pt. ID	Major Complications (≤7 days)	Device Used
	This Phase III pt. had pericardial effusion that required a pericardial window to drain.	NavAblator Only
	This Phase III pt. had a sinus node injury that "likely arose from lateral lesions near the SA Node.	REVELATION Tx and NavAblator

The two other Major Complications reported in this study occurred following procedures that did not include an isthmus lesion and so are not included in the table above.

Table A-7
Treatment Outcome Results at Six Months Relative to Baseline[1]
by Device Employed to Create the Lesion at the Isthmus Line

Outcome	Navablator* (n=28)	RevelationTx (n=17)	Other** (n=28)	Total (n=73)
Success[2]	21/28 (75.0)	16/17 (94.1)	26/28 (92.9)	63/73 (86.3)
Episode Reduction[3]	6.0 ± 10.8	8.6 ± 6.1	10.0 ± 10.6	8.2 ± 9.8
SF-36				
Physical Functioning	7.0 ± 18.8	9.6 ± 25.1	8.4 ± 18.3	8.1 ± 19.7
Role Physical	9.5 ± 50.2	21.9 ± 35.2	33.0 ± 38.5	21.2 ± 43.6
Role Emotional	3.4 ± 44.0	9.5 ± 65.9	19.0 ± 50.0	10.8 ± 51.0
Bodily Pain	7.4 ± 21.7	5.1 ± 31.6	5.3 ± 24.2	6.1 ± 24.8
General Health	-0.7 ± 17.8	2.6 ± 18.1	1.7 ± 14.9	1.0 ± 16.7
Vitality	6.3 ± 24.1	7.6 ± 20.5	16.1 ± 16.5	10.3 ± 20.9
Social Functioning	11.2 ± 24.8	8.8 ±25.3	9.8 ± 17.5	10.1 ± 22.1
Mental Health	2.5 ± 22.5	-3.1 ± 8.9	4.4 ± 19.9	1.9 ± 19.1
AFSS				
Episode Frequency	16.2 ± 27.6	26.2 ± 35.9	20.0 ± 28.6	19.8 ± 29.6
Episode Duration	14.3 ± 34.3	11.7 ± 47.3	7.7 ± 20.2	11.2 ± 32.0
Episode Severity	16.5 ± 29.9	24.8 ± 26.9	15.5 ± 37.3	17.6 ± 32.4
AFSS Total	16.2 ± 24.3	17.3 ± 24.7	12.5 ± 19.7	14.9 ± 22.2

* Includes 2 subjects treated with *REVELATION Tx* and *NavAblator*. ** *Includes 20 subjects treated with* REVELATION Tx or NavAblator as well as "Other".

[1] Six month value – baseline value; positive scores indicate improvement. These results do not include 8 subjects who did not have the isthmus line ablated

[2] Patient treatment success, 50+% reduction in episodes, freq/n, %

[3] mean ± SD

The data presented in Table A-7, above, illustrate that the six-month success rate for subjects treated with the NavAblator at the isthmus line was 75%, well above the success criterion. Rates for the REVELATION Tx and Other miscellaneous devices were 94.1% and 92.9%, respectively.

Overall clinically significant improvements (10+ points) are evident for all AFSS parameters and the total AFSS score, and for four of the eight SF-36 domains, i.e., role physical, role emotional, vitality and social functioning. However, there are no apparent consistent trends in the QOL results among the three different categories of this table. However, it should be noted that the differences observed may be random results from stratifying outcomes into subgroups (see: Yusuf, S. et al., Analysis and Interpretation of Treatment Effects in Subgroups of Patients in Randomized Clinical Trials. JAMA 266, No.1, p. 93-98, 1991).

Finally, it is important to remember that the NavAblator is part of a system and is not meant to be approved as a "stand-alone" device.

6. *Your clinical trial includes many variables, such as different devices, different ablation procedures performed, and different study protocols for different phases of the investigation. Please provide a statistical justification for pooling the data generated by the trial, given these variables in the study.*

Cardima does not believe that the study protocols differed between Phase IIb and Phase III in ways that affect outcomes or data collected or analyzed, since the patient selection criteria, study objectives and endpoints all remained unchanged. Similarly, the different devices (for treating the isthmus line) were intentional and intended to be part of a "system". The ablation procedures performed did not differ except that some lesions varied by patient, which is as it would be in normal clinical practice. The objective of creating the lesions was consistently the control of atrial fibrillation.

Cardima does not believe that these small differences significantly impact the demonstration of safety and effectiveness. The clinical trial was designed to measure frequency of AF on a per patient basis with each patient acting as his/her own control. In addition, the study endpoints and hypotheses reflect highly objective and reliable clinical measures. For these reasons, Cardima believes that any potentially significant biases which could adversely affect data analysis are minimized and ostensibly overcome by the inherent robustness of the clinical trial design, which was based fundamentally upon the recommendations to FDA from the Circulatory System Advisory Panel meeting on July 22, 1998 regarding the design of clinical trials to support premarket approval applications for cardiac ablation devices intended to treat atrial fibrillation.

Table A-8 presents a statistical overview of the primary outcome measures for this study by study phase. Overall, there are no striking differences nor evidence of trends of consistent modest differences between study phases. There are generally small and mixed differences between study phases for all of the Quality of Life (SF-36 and AFSS) parameters. One of the largest mean differences for subjects of the two phases was for role physical, but subjects from both study phases averaged clinically significant improvements. Both mean episode reduction and percentage successful six-month episode reduction slightly favored Phase IIb subjects. However, this difference could also be the result of patient selection.

Table A-8 - Treatment Outcome Results at Six Months Relative to Baseline[1] by Study Phase

Outcome	Phase IIb (n=31)	Phase III (n=46)	Total (n=77)
Success[2]	28/31 (90.3%)	37/46 (80.4%)	65/77 (84.4%)
Episode Reduction[3]	9.4 ± 10.5	6.7 ± 9.2	7.8 ± 9.8
SF-36			
Physical Functioning	5.5 ± 20.4	8.7 ± 18.8	7.4 ± 19.4
Role Physical	29.8 ± 37.9	16.5 ± 46.1	21.8 ± 43.3
Role Emotional	10.0 ± 51.2	13.0 ± 49.9	11.8 ± 50.1
Bodily Pain	-0.3 ± 24.5	11.7 ± 24.0	7.0 ± 24.7
General Health	3.7 ± 15.9	-0.2 ± 16.5	1.3 ± 16.3
Vitality	10.8 ± 19.3	11.2 ± 22.3	11.0 ± 21.0
Social Functioning	5.2 ± 19.6	15.2 ± 24.0	11.2 ± 22.8
Mental Health	3.2 ± 18.7	1.8 ± 18.8	2.4 ± 18.6
AFSS			
Episode Frequency	21.6 ± 30.6	18.8 ± 28.7	19.8 ± 29.3
Episode Duration	4.8 ± 20.1	16.4 ± 36.4	12.1 ± 31.1
Episode Severity	19.2 ± 34.2	17.2 ± 30.4	18.0 ± 31.7
AFSS Total	13.0 ± 18.8	16.6 ± 24.2	15.2 ± 22.2

[1] Six month value – baseline value; positive scores indicate improvement
[2] Patient treatment success, 50+% reduction in episodes, freq/n, %
[3] mean ± SD

7. *The secondary effectiveness endpoint of your clinical trial was improvement in quality of life (QOL) as measured by two instruments, the SF-36 and the Atrial Fibrillation Severity Scale, and measured at baseline and at various post-treatment time points. You provided the mean scores and standard error for the instrument scores at baseline, three month and six month follow-up. Please provide the number of patients who achieved a clinically significant improvement or worsening from baseline to the six month follow-up for the total group and for the subgroups of patients stratified by baseline episode rate. Please explain in detail how the QOL questionnaires were administered. Also, please address adjustment for placebo effect, given that the clinical study was consisted (sic) of a single arm and was unblinded.*

The number of patients who achieved a clinically significant improvement or worsening from baseline to the six-month follow-up stratified by baseline episode rate and for the total group is presented in Table A-9 and Table A-10, respectively.

Table A-9 provides the frequencies and percentages of subjects with six-month clinically significant improvements in QOL parameters according to baseline episode frequency category. Overall, at least 40 percent of the subjects had clinically significant improvements for four of the eight SF-36 domains, such as, role physical, bodily pain, vitality, and social functioning. The overall range of percentages of subjects with clinically significant improvement across the eight domains was 29.2% to 53.4%. More pronounced yet, at least 40 percent of the subjects had clinically significant improvement for all three AFSS component measures and for the total AFSS score with the largest percentages for episode frequency (60.3%) and episode severity (58.8%). There are generally small and mixed differences among categories for all of the quality of life (SF-36 and AFSS) outcomes. There are no striking differences, nor evidence of trends of consistent modest differences, among categories of baseline episodes in the results of this table.

Table A-9 - Six Month SF-36 and AFSS Clinically Significant Improvement (increase by 10+ points) by Baseline Episode Frequency

Measurement Scale	3-4 episodes (freq/n, %)	5-9 episodes (freq/n, %)	10-19 episodes (freq/n, %)	20+ episodes (freq/n, %)	Total (freq/n, %)
SF-36					
Physical Functioning	8/19, 42.1	9/30, 30.0	5/13, 38.5	1/7, 14.3	23/69, 33.3
Role Physical	5/21, 23.8	14/31, 45.2	8/14, 57.1	3/7, 42.9	30/73, 41.1
Role Emotional	8/21, 38.1	7/30, 23.3	6/13, 46.2	4/7, 57.1	25/71, 35.2
Bodily Pain	12/21, 57.1	12/31, 38.7	6/15, 40.0	3/7, 42.9	33/74, 44.6
General Health	7/21, 33.3	3/30, 10.0	7/14, 50.0	4/7, 57.1	21/72, 29.2
Vitality	11/20, 55.0	15/31, 48.4	8/15, 53.3	5/7, 71.4	39/73, 53.4
Social Functioning	11/21, 52.4	17/30, 56.7	7/15, 18.9	2/7, 28.6	37/73, 50.7
Mental Health	10/21, 47.6	4/30, 13.3	5/15, 33.3	2/7, 28.6	21/73, 28.8
AFSS					
Episode Frequency	7/16, 43.8	17/26, 65.4	8/14, 57.1	6/7, 85.7	38/63, 60.3
Episode Duration	6/16, 37.5	9/25, 36.0	6/12, 50.0	4/7, 57.1	25/60, 41.7
Episode Severity	13/19, 68.4	15/29, 51.7	8/13, 61.5	4/7, 57.1	40/68, 58.8
AFSS Total	8/16, 50.0	13/25, 52.0	6/11, 54.6	5/7, 71.4	32/59, 54.2

In contrast to above, the Table A-10, below provides the frequencies and percentages of subjects with six-month clinically significant *decreases* in QOL parameters according to baseline episode frequency category. The percentages of subjects overall with clinically significant decreases in QOL are small, ranging 11.0 to 33.3 for the SF-36 domains and all being less than 20% for the AFSS measures and total AFSS score. Because of the small numbers of subjects with clinically significant decreases generally, it is difficult to assess these results for evidence of trends of consistent differences among categories of baseline episodes.

Table A-10 - Six Month SF-36 and AFSS Clinically Significant Decline (decrease by 10+ points) by Baseline Episode Frequency (freq/n, %)

Measurement Scale	3-4 episodes (freq/n, %)	5-9 episodes (freq/n, %)	10-19 episodes (freq/n, %)	20+ episodes (freq/n, %)	Total (freq/n, %)
SF-36					
Physical Functioning	3/19, 15.8	7/30, 23.3	2/13, 15.4	1/7, 14.3	13/69, 18.8
Role Physical	3/21, 14.3	4/31, 12.9	0/14, 0.0	1/7, 14.3	8/73, 11.0
Role Emotional	2/21, 9.5	6/30, 20.0	3/13, 23.1	1/7, 14.3	12/71, 16.9
Bodily Pain	5/21, 23.8	9/31, 29.0	4/15, 26.7	2/7, 28.6	20/74, 27.0
General Health	5/21, 23.8	17/30, 56.7	2/14, 14.3	0/7, 0.0	24/72, 33.3
Vitality	6/20, 30.0	4/31, 12.9	0/15, 0.0	1/7, 14.3	11/73, 15.1
Social Functioning	3/21, 14.3	5/30, 20.0	4/15, 26.7	2/7, 28.6	14/73, 19.2
Mental Health	5/21, 23.8	8/30, 26.7	1/15, 6.7	0/7, 0.0	14/73, 19.2
AFSS					
Episode Frequency	4/16, 25.0	2/26, 7.7	3/14, 21.4	0/7, 0.0	9/63, 14.3
Episode Duration	2/16, 12.5	5/25, 20.0	2/12, 16.7	1/7, 14.3	10/60, 16.7
Episode Severity	3/19, 15.8	6/29, 20.7	3/13, 23.1	1/7, 14.3	13/68, 19.1
AFSS Total	2/16, 12.5	3/25, 12.0	3/11, 27.3	0/7, 0.0	8/59, 13.6

Cardima believes that obvious or subtle potential placebo effects are minimized, especially when comparing differences in pre- vs. post- procedure QOL measures. However, to explore the possibility of a placebo effect on episode reduction and to investigate the internal validity of all of these measures, we have statistically characterized and evaluated possible associations between and among QOL outcomes and change in frequency of AF.

Table A-11, below provides all possible pair-wise Pearson correlation coefficients among all QOL parameters and episode reduction.

Virtually all of the correlation coefficients of this table are positive and the few negative coefficients do not exceed –0.10. Over one-half (43) of the 78 correlations in this table are significant at 0.05, and many (32) are significant 0.01. Twelve of the correlations are highly significant, $p<0.0001$. Most importantly, six-month decreases in episode frequency were significantly and directly associated with improvements in total AFSS score and AFSS past three-month episode frequency, and SF-36 domains of vitality and general health. Improvement from treatment may perhaps be observed not only in episode frequency reduction, but also in reductions in AFSS episode duration and severity. Thus, also of note might be the significant associations

between AFSS episode duration and Role Physical and Role Emotional, and episode severity and role emotional and mental health. The total AFSS score change at six months relative to baseline was also significantly and directly correlated with SF-36 changes in the domains of Role Physical, Role Emotional, Vitality, and Mental Health. These findings support the internal validity and general positive outcomes of this study.

Table A-11 - Pearson's Correlation Coefficients for Baseline to 6 Month Change in SF-36, AFSS, and Number of Documented Symptomatic Episodes (coefficient, p-value, n)

	PF	RP	RE	BP	GH	V	SF	MH	EF	ED	ES	AFSS
SF-36												
Physical Functioning	- - -											
Role Physical	0.20 0.08 74											
Role Emotional	0.29 0.014 73	0.46 0001* 76										
Bodily Pain	0.35 0.002 74	0.17 0.13 78	0.44 0001* 76									
General Health	0.36 0.002 72	0.45 0001* 76	0.34 0.003 74	0.35 0.002 77								
Vitality	0.36 0.002 73	0.56 0001* 77	0.50 0001* 75	0.32 0.005 78	0.44 0001* 76							
Social Functioning	0.19 0.10 73	0.33 0.003 77	0.43 0001* 75	0.31 0.006 78	0.30 0.007 77	0.45 0001* 77						
Mental Health	0.15 0.22 73	0.33 0.003 77	0.34 0.003 75	0.15 0.20 78	0.42 0.001 76	0.55 0001* 77	0.29 0.012 77					
AFSS												
Episode Frequency	0.09 0.49 63	0.20 0.11 65	0.04 0.76 64	0.03 0.81 66	0.16 0.20 64	0.33 0.007 65	0.19 0.14 65	0.32 0.008 66				
Episode Duration	0.11 0.39 61	0.28 0.029 63	0.37 0.003 62	0.17 0.18 64	0.22 0.08 62	0.19 0.14 63	0.26 0.041 63	0.19 0.12 65	0.36 0.004 63			
Episode Severity	0.01 0.92 71	0.15 0.21 73	0.29 0.013 72	0.04 0.73 73	0.08 0.51 71	0.09 0.43 72	0.08 0.49 72	0.30 0.01 72	0.32 0.01 65	0.39 0.001 63		
AFSS Total	0.14 0.27 60	0.36 0.004 62	0.34 0.007 61	0.14 0.28 62	0.24 0.07 60	0.29 0.02 61	0.20 0.12 61	0.40 0.001 62	0.77 0001* 62	0.75 0001* 62	0.74 0001* 62	
Episode Change	-0.08 0.53 67	0.15 0.21 71	0.15 0.23 69	-0.05 0.65 72	0.28 0.017 70	0.27 0.024 71	-0.07 0.57 71	0.17 0.16 71	0.32 0.011 61	0.14 0.30 61	0.20 0.11 66	0.30 0.025 57

*=p< 0.0001

Finally, although the number of six-month failures available for statistical comparisons is small (n=12), Table A-12, below is presented to show that patients who were considered treatment successes at six months also tended to have higher percentages with clinically significant improvements for the SF-36 and AFSS quality of life measures.

Table A-12 - Six Month SF-36 and AFSS Clinically Significant Improvement (increase by 10+ points) by Episode Reduction Success

Outcome	Treatment Status			
	Success		Failure	
	freq/n	%	freq/n	%
SF-36				
Physical Functioning	20/55	36.4	3/12	25.0
Role Physical	26/59	44.1	3/12	25.0
Role Emotional	23/57	40.4	2/12	16.7
Bodily Pain	30/60	50.0	2/12	16.7
General Health	19/58	32.8	2/12	16.7
Vitality	33/59	55.9	5/12	41.7
Social Functioning	30/59	50.9	5/12	41.7
Mental Health	17/59	28.8	4/12	33.3
AFSS				
Episode Frequency	30/49	61.2	7/12	58.3
Episode Duration	21/46	45.6	3/12	25.0
Episode Severity	34/54	63.0	5/12	41.7
AFSS Total	27/45	60.0	4/12	33.3

Quality of Life questionnaires were administered by the study coordinator for each site at the time of the scheduled assessment interval visit that required a QOL assessment. The questionnaires were distributed to the subject and generally were completed at that visit. Some patients requested the opportunity to complete the questionnaires from home because they were too fatigued from the stress test to complete the form. If the subject did not mail in the form, the coordinator would complete the form for the patient in a telephone interview where the subject was asked for the answer to each question.

The data from the completed questionnaires were entered into the Cardima database by independent data entry personnel and the results evaluated by contract biostatisticians.

In summary, Cardima believes that it is highly unlikely that placebo effect could be attributable for the positive results of this study given the magnitudes, statistical and clinical significance, and broad range of effects observed in these subjects.

8. *The acute procedural endpoint was dropped from the clinical trial protocol between phases IIb and III. Please explain how the investigators in phase III determined when they had produced effective lesions. Please clarify whether you intended the ablation procedure to be strictly anatomically based. Please explain whether you intend to recommend measurement of bi-directional block to assess the adequacy of the tricuspid isthmus ablation line.*

The acute procedural endpoint for this study was the same in both Phase IIb and in Phase III. That endpoint was described as

> 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 measurement of pacing thresholds (c) was eliminated between Phase IIb and Phase III because of the increase in fluoro time required to accomplish that measurement. Electrogram evaluations (a and b) remained in tact consistently throughout both phases of the study.

While this procedure is generally intended to be an anatomical procedure and investigators look for a decrease in electrogram amplitudes to determine if they have an effective lesion and, at the isthmus line, they look for electrogram changes such as split potentials, the organization of atrial signals upon delivery of linear lesions, or assess bi-directional block.

However, the formal measurement of bi-directional block at the isthmus line requires the use of a coronary sinus catheter or Halo type catheter. Cardima will recommend the use of one or the other, rather than exclusively one, to be consistent with clinical practice.

9. *The primary effectiveness endpoint of the trial was decrease in frequency of atrial fibrillation episodes from baseline to 6 months follow-up. This was assessed by transtelephonic event recordings which were described as "mandatory" weekly in months three and six. This is not described in the investigational protocol. Please provide an assessment of compliance with the transtelephonic recordings per patient. Explain whether any other method was established and used to determine if patients were having symptoms not reported.*

   Patients were followed by the event monitoring service for compliance. A patient who failed to transmit a weekly recording was contacted directly by the monitoring service and a transmission was requested. Hard copies of the transmission records were forwarded to both the investigational site and to Cardima. Based upon the transmission records and the reports of the study monitors, compliance with transmission was generally good.

   Most importantly, six-month decreases in episode frequency were significantly and directly associated with improvements in total AFSS score and AFSS past three-month episode frequency and SF-36 domains of vitality and general health, adding to face validity of these findings reported in response to deficiency #5, above. Improvement from treatment may perhaps be observed not only in episode frequency reduction, but also in reductions in AFSS episode duration and severity.

   In addition to weekly transmissions, patients may report symptoms during office visits and any such symptoms are recorded at each assessment interval on Case Report Forms (e.g., CRF# 31 and 32, Arrhythmia Events, which also collect data regarding hospitalization for cardiac arrhythmias) and on the AFSS Quality of Life Questionnaire at 3 months and 6 months.

10. *Please provide details of the baseline monitoring period per patient. This should include number of recorded events and their electrocardiographic diagnosis, such as sinus tachycardia, atrial fibrillation, etc. Please add the calculation of the percentage of recordings per patient that were diagnosed to be atrial fibrillation.*

    These details are represented by source documents for data that has been collected, verified, and reported on the Case Report Forms (CRFs) for this study. The source documentation is extensive and complex. The details of episode frequency monitoring at any interval are derived from records from the cardiac event transmission monitoring service. For both Phase IIb and Phase III heart cards, portable cardiac event monitoring devices are used to record symptoms. When those symptoms are transmitted telephonically to the monitoring service, the electrograms are recorded electronically and the resulting electrocardiogram strips are reviewed for evidence of cardiac irregularities. These strips are also annotated to include verbal reports of symptoms from the caller at the time of transmission. The technical staff of the monitoring service makes an interpretation of the nature of the cardiac event at

the time of the transmission and these results are entered into the electronic database maintained by the service. Hard copies of the reports with the interpretation are forwarded to both the site and the sponsor.

In addition, the transmitted electrograms are reviewed and confirmed by the monitoring service's staff cardiologist. The cardiologist issues a separate report and creates a separate record of his/her interpretation of the strips. A hard copy report of this separate interpretation is forwarded to both the site and the sponsor. Generally the cardiologist's interpretation and the technician's interpretation agree. On those occasions when they disagree, the cardiologist's interpretation takes precedent, but the new interpretation is not incorporated into the electronic database maintained by the monitoring service.

The number of recorded events that are "diagnosed" electrocardiographically by the as AF is documented on the CRF for Arrhythmia Events (e.g., CRF #31). Part of the data verification performed by the clinical research coordinator at each site and by the sponsor's monitors is to confirm that the information recorded on CRFs correlates exactly with the data reported by the event monitoring service.

This practice provides considerable assurance that the records accurately reflect the data collected by the event monitoring service.

However, during this investigation, Cardima changed monitoring services. Thus there are two different sources and types of electronic records, one of which has been "frozen" so that the data cannot be copied or manipulated to re-tabulate or re-format. The second monitoring service had a "crash" of its computer system resulting in the loss of record for two patients, but not until after the hard copy had been forwarded to Cardima and the investigational site.

In addition, there was one patient whose baseline records include one electrocardiogram collected from a 12-lead EKG done during a hospital visit that occurred during the baseline monitoring period.

Consequently, in order for Cardima to provide the details requested and conduct a calculation on the percentage of transmissions that resulted in atrial fibrillation episodes diagnoses per patient, multiple data sources, including paper records must be compiled and tallied. This effort is under way but will require considerable resources and additional time. The final results will be forwarded under separate cover in the coming weeks.

11. *Based on our review of your clinical summary, it appears that you included the 11 patients who withdrew from the study after having an ablation procedure in your assessment of effectiveness. Please justify using this approach, especially for the 6 patients who were subsequently treated with a pacemaker and the 2 patients who had a MAZE procedure after the ablation procedure. Please provide the identifier numbers for these patients and the details of their treatment in your effectiveness assessment.*

The procedural effectiveness is primarily assessed based upon atrial fibrillation outcome. Patients who were subsequently treated with a pacemaker following AV nodal ablation for atrial fibrillation would be included in the effectiveness assessment for any assessment interval that occurred prior to their withdrawal from the study. Each effectiveness assessment interval necessarily excluded any patient who had withdrawn from the study at or before that interval.

In this regard, of the 11 subjects listed in the Original PMA submission (P020039), five (5) subjects did not withdraw from the study until after the 6 month follow up interval and, therefore, would be included in an effectiveness analysis at all FU intervals. Four (4) other subjects withdrew after the 3-month FU interval and would have been included in the effectiveness analysis for the 3-month interval. The remaining two withdrew before the 3 months interval and would be excluded from both the 3-month and the 6-month intervals. Therefore, none of these subjects was included in the pivotal six-month effectiveness analysis.

One of the five subjects who withdrew after the 6 month FU, had a pacemaker inserted for apparent sick sinus syndrome, not atrial fibrillation. Because a pacemaker does not control atrial fibrillation this patient continued in the study along with eight (8) other patients who qualified for study entry with pacemakers already in place.

It must be noted that the Original PMA submission (P020039) contained an error in its listing of subjects who withdrew from the study. Table F-11, on page 59 in Volume 7 of that submission, listed 6 subjects who withdrew because of pacemaker insertions. One of those was subject [redacted] This should have been identified as [redacted] did not withdraw from the study because of pacemaker insertion and, as of the date of this submission, the reason for withdrawal is unknown.

Table A-13 presents these 11 study subjects by their identifiers, date indication for pacemaker insertion and study status.

Table A-13 - Subject Withdrawal by Study Interval.

Pt. ID	Date of Tx	Date Last FU Interval	Reason	Date of Reason
	05/27/99	06/02/00[1]	AVN / PPM	>06/02/00
	07/08/99	07/05/00[1]	Maze	10/04/00
	03/15/00	09/14/00[2]	Maze	>09/14/00
	04/30/99	08/03/99[3]	AVN / PPM	10/13/99
	06/03/99	09/20/99[3]	AVN / PPM	10/06/99
	07/06/99	--[5]	AVN / PPM	07/19/99
	08/29/01	01/08/02[2]	DDD (tachy-brady)	01/10/02
	06/21/00	09/26/00[3]	None Stated	--
	12/03/01	05/03/02	PPM for SSS	12/04/01
	07/16/01	10/29/01[3]	None Stated	--
	12/19/01	01/16/02[4]	Moved out of State	--

[1] 12-month FU [2] 6-month FU [3] 3-month FU
[4] 1-month FU, (procedural outcome determined to be "success")
[5] Not Included in effectiveness analysis at any time point

12. *You provided a list of all the adverse events reported by the investigators, arranged alphabetically by adverse event. Please provide a list of adverse events grouped by patient.*

Listing of AEs that were reported by the sites as "possibly" or "probably" related to either the device or the procedure by Pt ID are provided in Table A-15, Appendix A-1. All reported AEs regardless of relationship to device or procedure are included as part of the clinical update in Table F-58, Appendix F-1.

13. *Table F-18, page 64 of your submission, shows the baseline number of symptomatic atrial fibrillation episodes that occurred in the patient population of your study. It appears that there may be two groups of patients, grouped around 3-4 episodes per month and again at 10-19 episodes per month. FDA is concerned that this bimodal distribution may represent a difference in the patient's disease process. Please justify the pooling of all these patients.*

As illustrated in Table A-14, below, there is no apparent trend in treatment success according to baseline episode frequency category. As requested, for purpose of examining subject outcome according to number of baseline episodes, we have grouped baseline episodes into the following categories: 3-4, 5-9, 10-19, 20+.

Of the subjects with six-month episode data, nearly one third (23/77, 29.9%) of the subjects had 10 or more symptomatic episodes during the 30-day baseline monitoring, with somewhat similar percentages of subjects having fewer than five episodes (23/77, 29.9%) and 5-9 episodes (31/77, 40.3%).

The results below for baseline to six-month changes do not indicate any apparent trends in outcome related to baseline episode frequency category except for episode reduction, where subjects with higher numbers of baseline episodes had larger reductions in number of episodes and larger improvements in vitality, and AFSS three month episode frequency in the three months prior to the six-month visit. These associations are not unexpected because patients with more serious health conditions are eligible for greater improvements. Also, it should be noted that the differences observed may also be, to some degree, random results from stratifying outcomes into subgroups (see : Yusuf, S. et al. Analysis and Interpretation of treatment Effects in Subgroups of patients in Randomized Clinical trials, JAMA 266, No. 1, p. 93-98, 1991.).

Table A-14 - Treatment Outcome Results at Six Months Relative to Baseline[1] by Baseline Episode Frequency

Outcome	3-4 episodes (n=23, 29.9%)	5-9 episodes (n=31, 40.3%)	10-19 episodes (n=16, 20.8%)	20+ episodes (n=7, 9.1%)	Total[4] (n=77, 100.0%)
Success[2]	20/23 (87.0%)	24/31 (77.4%)	14/16 (87.5%)	7/7 (100.0%)	65/77 (84.4%)
Episode Reduction[3]	3.1 ± 0.9	4.1 ± 4.1	10.9 ±4.6	32.6 ± 13.2	7.8 ± 9.8
SF-36					
Physical Functioning	9.7 ± 19.3	5.5 ± 19.1	6.9 ± 18.9	-4.3 ± 15.6	7.4 ± 19.4
Role Physical	3.6 ± 42.0	24.2 ± 42.6	37.5 ± 40.0	14.3 ± 40.5	21.8 ± 43.3
Role Emotional	14.3 ± 46.6	7.8 ± 46.1	7.7 ± 69.6	33.3 ± 50.9	11.8 ± 50.1
Bodily Pain	10.5 ± 29.1	2.9 ± 21.9	5.9 ± 24.2	5.4 ± 28.0	7.0 ± 24.7
General Health	1.4 ± 17.1	-7.0 ± 13.0	7.5 ± 13.0	7.1 ± 5.7	1.3 ± 16.3
Vitality	8.0 ± 21.0	8.2 ± 19.3	18.3 ± 20.1	17.9 ± 21.9	11.0 ± 21.0
Social Functioning	15.5 ± 24.0	11.3 ± 21.4	9.2 ± 22.9	7.1 ± 32.2	11.2 ± 22.8
Mental Health	5.3 ± 22.4	-3.2 ± 15.2	8.8 ± 23.1	6.9 ± 7.2	2.4 ± 18.6
AFSS					
Episode Frequency	6.3 ± 22.2	20.8 ± 26.8	23.6 ± 37.7	34.3 ± 26.4	19.8 ± 29.3
Episode Duration	21.4 ± 35.8	7.4 ± 32.8	7.1 ± 26.2	18.4 ± 35.7	12.1 ± 31.6
Episode Severity	18.1 ± 28.3	17.2 ± 32.1	23.9 ± 34.8	20.6 ± 34.8	18.0 ± 31.7
AFSS Total	12.7 ± 19.5	13.5 ± 22.8	13.6 ± 24.1	25.3 ± 27.3	15.2 ± 22.2

[1] Six month value – baseline value; positive scores indicate improvement

[2] Patient treatment success, 50+% reduction in episodes, freq/n, %

[3] mean ± SD

[4] Does not include 5 subjects with ambiguous number of baseline episodes.

Figures A-1 and A-2 illustrate the results summarized in Table A-14.

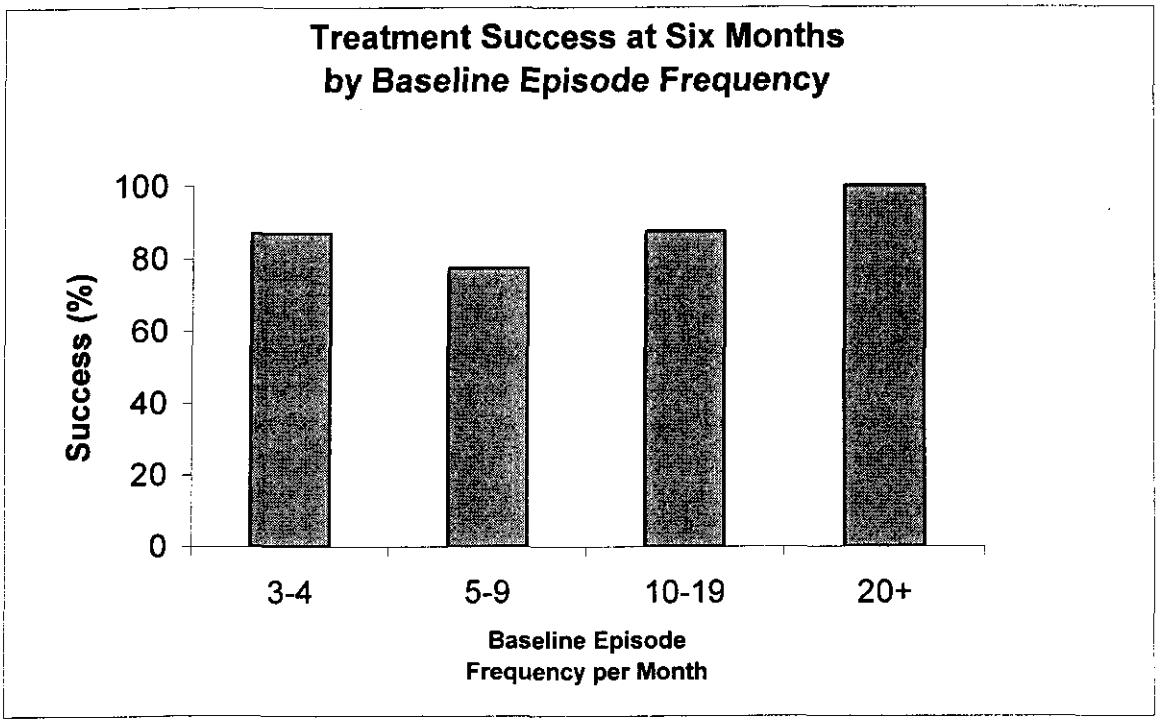


Figure A-1, Treatment Success at Six Months by Baseline Episode Frequency

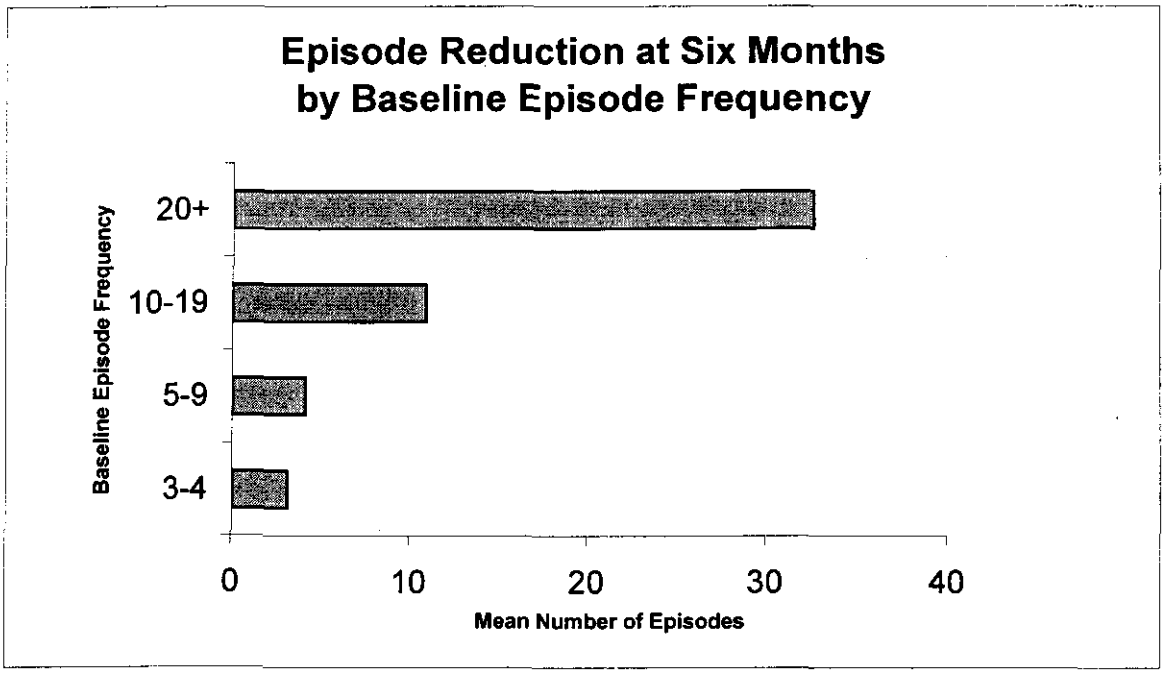


Figure A-2, Episode Reduction at Six Months by Episode Frequency

14. *While 80 patients (as required by sample size process) have been followed for six months, the remaining 19 enrolled have not. All patients enrolled in the study should have been followed for at least six months. Please submit an updated clinical report that includes study results from these addition (sic) 19 patients.*

    Cardima continues to enroll patients in this study so all patients enrolled in the study will not have been followed for 6 months until 6 months after enrollment stops. However, an updated report of the clinical data submitted with the original PMA, including results from all treated patients and baseline and all available procedural data from 18 additional patients treated since the data were compiled for the original PMA are included with this submission as Appendix 3, Volume 2.

15. *The adequacy of the sample size of 80 patients depends on the clinically sufficient narrowness of the 95% confidence intervals for the observed parameter estimates. Please provide clinical justification. Were a priori acceptable differences from the estimates established during the sample size estimation process to assure sufficiently narrow confidence intervals?*

    At the suggestion of FDA CDRH biostatistical staff (Dr. Gary Kramer), confidence intervals were employed to illustrate the adequacy of the sample size by providing a clinically acceptable range of precision. As the ultimate success rate was unknown, success rates of 40%, 50%, (most conservative, largest SE) and 70% were used to predict the standard errors of the success rate estimates. These standard errors were 0.055, 0.056 and 0.051 respectively. These values were deemed to be clinically acceptable degrees of precision for estimating treatment success. This success rate was defined as the percentage of patients with a clinically meaningful percentage reduction (i.e., 75% for 3-4 baseline episodes, 50% for 5+ baseline episodes). It is also important to recognize that statistically significant improvements in outcome were generally realized to a high degree of statistical significance for the primary outcome of episode reduction and for many of the quality of life measures.

    The achieved sample size is actually 25% greater than originally targeted, and the six-month success rate of 85.4% is higher than expected. The standard error for this success rate is 0.039, approximately one-third better than the possible standard error of 0.056 that was considered clinically acceptable at the inception of Phase III. The 95% confidence interval for the success rate at six months in the updated clinical section is 76.1%, 91.4%.

    We believe that these effectiveness results are consistent with the guidelines established by the Circulatory System Devices Advisory Panel at its meeting on July 22, 1998. Specifically, the Panel recommended to FDA that demonstrating a 75% reduction in the frequency of symptomatic AF episodes should be considered a clinically meaningful improvement in patient outcome.

At that same meeting, the Panel determined that there was not an appropriate control group that would allow for an ethical or feasible clinical trial design (i.e., randomizing to antiarrhythmic drug therapy was considered impractical because patients considered for enrollment were already supposed to have failed at least 2 such drugs). As a result, the Panel recommended that it would be necessary for a sponsor to qualitatively evaluate device safety in relation to device effectiveness by using a risk/benefit approach rather than a quantitative approach.

16. *It is unclear that the paired t-tests were performed properly; data should be paired based on patient, not number of episodes. Please either justify your analyses or provide revised analyses based on data paired by patient.*

In all determinations of statistical significance the paired values within individual subject were indeed employed. Further, the actual mean paired differences at three and six months for number of symptomatic episodes have been added to the narrative. Pairing of baseline and follow up values for study outcomes is a fundamental feature of this study design, provides a measure of "control", and improves statistical power.

Statistical significance values for change in QOL and number of episodes at three and six months are derived using the baseline and follow up outcome results paired within individual subject employing the paired t-test. This clarification has also been included in the updated clinical section, Appendix 3, Volume 2.

17. *Please provide descriptive and inferential analyses by clinical site. Also, provide appropriate analyses by patient demographics.*

Tables A-15 and A-16, below provide the six-month treatment outcomes by gender and age group. Overall, there are no striking differences or evidence of trends of consistent differences between groups in the results of these tables. The differences observed between genders or age groups may be random results from stratifying outcomes into subgroups (see: Yusuf, S. et al. Analysis and Interpretation of treatment Effects in Subgroups of patients in Randomized Clinical trials, JAMA 266, No. 1, p. 93-98, 1991).

Table A-15 - Treatment Outcome Results at Six Months Relative to Baseline[1] by Gender of Subject

Outcome	Male (n=63)	Female (n=14)	Total (n=77[4])
Success[2]	53/63 (84.1%)	12/14 (85.7%)	65/77 (84.4%)
Episode Reduction[3]	8.1 ± 10.4	6.6 ± 6.7	7.8 ± 9.8
SF-36			
Physical Functioning	8.8 ± 20.1	3.1 ± 16.8	7.4 ± 19.4
Role Physical	26.7 ± 39.9	6.6 ± 50.6	21.8 ± 43.3
Role Emotional	-1.8 ± 49.2	16.4 ± 51.5	11.8 ± 50.1
Bodily Pain	6.8 ± 24.4	7.5 ± 26.2	7.0 ± 24.7
General Health	0.2 ± 15.1	4.7 ± 19.5	1.3 ± 16.3
Vitality	14.0 ± 21.4	1.8 ± 17.3	11.0 ± 21.0
Social Functioning	10.8 ± 22.1	12.5 ± 25.4	11.2 ± 22.8
Mental Health	1.7 ± 19.4	4.4 ± 16.5	2.3 ± 18.6
AFSS			
Episode Frequency	18.1 ± 30.7	26.4 ± 23.1	19.8 ± 29.3
Episode Duration	11.1 ± 32.8	15.3 ± 27.7	12.1 ± 31.6
Episode Severity	16.1 ± 30.6	24.2 ± 35.6	18.0 ± 31.7
AFSS Total	13.2 ± 21.5	22.8 ± 23.7	15.2 ± 22.2

[1] Six month value – baseline value; positive scores indicate improvement
[2] Patient treatment success, 50+% reduction in episodes, freq/n, %
[3] mean ± SD
[4] Does not include 5 subjects with ambiguous number of baseline episodes.

Table A-16 - Treatment Outcome Results at Six Months Relative to Baseline[1] by Age Group of Subject

Outcome	Age ≤ 50 (n=20)	Age > 50 (n=57)	Total (n=77[4])
Success[2]	18/20 (90.0%)	47/57 (82.5%)	65/77 (84.4%)
Episode Reduction[3]	9.0 ± 11.4	7.4 ± 9.2	7.8 ± 9.8
SF-36			
Physical Functioning	11.8 ± 16.6	5.9 ± 20.2	7.4 ± 19.4
Role Physical	25.0 ± 38.0	20.7 ± 45.2	21.8 ± 43.3
Role Emotional	23.3 ± 55.2	7.7 ± 48.0	11.8 ± 50.1
Bodily Pain	8.1 ± 29.9	6.6 ± 23.0	7.0 ± 24.7
General Health	3.4 ± 14.7	0.6 ± 16.8	1.3 ± 16.3
Vitality	15.2 ± 22.9	9.6 ± 20.4	11.0 ± 21.0
Social Functioning	10.5 ± 20.9	11.4 ± 23.5	11.2 ± 22.8
Mental Health	11.4 ± 24.5	-0.8 ± 15.2	2.3 ± 18.6
AFSS			
Episode Frequency	19.4 ± 28.6	20.0 ± 29.8	19.8 ± 29.3
Episode Duration	13.4 ± 30.1	11.5 ± 32.4	12.1 ± 31.6
Episode Severity	25.1 ± 33.3	15.4 ± 31.1	18.0 ± 31.7
AFSS Total	17.2 ± 21.4	14.4 ± 22.6	15.2 ± 22.2

[1] *Six month value – baseline value; positive scores indicate improvement*
[2] Patient treatment success, 50+% reduction in episodes, freq/n, %
[3] mean ± SD
[4] Does not include 5 subjects with ambiguous number of baseline episodes.

In addition to gender and age group, the statistical analysis output from SAS programs for the same outcomes of these tables by investigational site is provided in Table A- 21, Appendix A-1, Volume 1.

18. Please address the following issues related to the Customer Experience Reports, supplied in Table F-43, page 111 in Volume 1 of the PMA:

a. You report ID 2002000261, which occurs on both pages 117 and 118 at two different cites (General Hospital Center at Passaic and Inova Fairfax Hospital). This suggests that the ID numbers are not unique to a specific event or procedure. Please describe how these Customer Experience Reports IDs are identified and tracked.

Cardima's customer experience ID numbers are unique and are established in consecutive order from the first report, prefaced by the year in which the report was received. That is, report ID# 2002000261 is the 261st report ever received at Cardima and it was received in the year 2002. The report numbers listed on page 118 reflect a typographical error duplicating the reports listed on page 117. The correct report ID#s for those reports listed on page 118 have been entered and the revised Table F-43 from page 118 is presented below as a new Table A-17.

b. For the reports that generated corrective actions, please confirm that these corrective actions were implemented. Please also confirm whether the manufacturing module (M004) reflects the updated processes containing the corrective actions. Finally, please provide a cross reference that calls out where the corrective actions are implemented in the manufacturing module.

Reports that generated corrective actions are listed in Table A-18. All corrective actions listed have been implemented and were implemented prior to the submission of M004.

The Manufacturing Module (M004) reported the name and number of the documents used in the manufacturing processes. However, the contents of those documents and the details of the processes themselves are not represented in detail by the documents included in M004. M004 presented Level II documents and manufacturing processes are largely Level III and Level IV documents. The identify of those documents was represented in M004, but not the revision level or the details of their contents. Therefore, the contents of the manufacturing module would not change based upon the changes resulting from any corrective actions affecting them.

Table A-17, Customer Experience Reports - NavAblator

ID	Failure Mode	Impact on Patient	Location/ Site	Date of Event	Corrective Action/Mitigation
2001000	Handle did not deflect tip. The NavAblator, when tested outside of the patient, would not deflect more than 90 degrees.	No Impact	Lankenau Hospital	5/30/2001	Investigation found set screw for pull wire assembly set short, not permitting full deflection. The manufacturing processes were reviewed with all employees who assemble the NavAblator.
2001000	Handle did not deflect tip. NavAblator would not fully deflect.	No Impact	Inova Fairfax Hospital	6/8/2001	Investigation found set screw for pull wire assembly set short, not permitting full deflection. The manufacturing processes were reviewed with all employees who assemble the NavAblator.
2001000	NavAblator has adhesive on shaft in the area over the product.	No Impact	n/a	10/31/2001	Packaging included adhesive strip over top of tray to prevent device from coming out of tray. In some cases residue from this adhesive strip adhered to surface of shaft. No customer field reports have been received on this but a Cardima rep noticed it on a few occasions. A new tray that mitigates the need for such a retaining device has been developed for the NavAblators and NAVIPORTS (9F and 10F)

36

Table A-18 Customer Experience Reports That Resulted in Corrective Actions

Report ID #	Description	Corrective Action
1999000090; 1999000093; 1999000094	REVELATION Tx "sticks" inside Naviport	Manufacturing process for REVELATION Tx catheter updated to "re-flow" THV to assure more robust integration of laminate to catheter shaft
1999000091 and may have also included 1999000090	Coagulum formed on electrodes on ablation catheter	This was considered to be a training issue regarding the gradual increase of RF temperature during EP ablation to minimize coagulum. This training was incorporated into all new site initiations as sites were added, but at the time of this report, there were only 3 investigational sites, so no further action was taken.
1999000113; 1999000123	Electrode wire failures on ablation catheter	Improve post-soldering cleaning process to assure no process residuals remain that could corrode wires.

AGENDA
CIRCULATORY SYSTEM DEVICES PANEL
May 29, 2003

Gaithersburg Holiday Inn, Walker/Whetstone room, 2 Montgomery Village Avenue, Gaithersburg, MD

9:00 – 5:00	**PMA Discussion, Recommendations, and Voting**

9:00 a.m. **Call to Order** **Warren K. Laskey, M.D., Acting Chairperson**

9:05 – 9:30a.m. **Office of Surveillance and Biometrics Presentation**
"Diathermy Interactions with Implanted Leads and Implanted Systems with Leads"
Marian Kroen, OSB/Issues Management Staff

9:30 – 10:00 a.m. ***Open Public Session***

10:00 – 11:00 a.m. **Sponsor Presentation: Cardima, Inc.**
P020039, Revelation Tx & NavAblator Catheter System

11:00 – 11:15 a.m. **Questions and Answers**

11:15 – 11:30 a.m. **Break**

11:30 – 12:30 p.m. **FDA Presentation**

12:30 – 12:45 p.m. **Questions and Answers**

12:45 p.m. **Adjourn – Break for Lunch**

1:45 – 2:45 p.m. **Call to Order**

2:45 – 3:45 p.m. **Open Committee Discussion** **Warren K. Laskey, M.D.**

3:45 – 4:00 p.m. **Break**

4:00 – 5:00 p.m. ***Open Public Session***
FDA Comments
Sponsor Comments

Recommendations & Vote **Warren K. Laskey, M.D.**

5:00 p.m. **Adjourn**

OPEN PUBLIC HEARINGS*

Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee.

Ms. Wood will present the speakers who have requested time for presentation to the Panel. After the scheduled speakers have spoken, the Chair may ask them to remain if the committee wishes to question them further. Dr. Laskey will recognize unscheduled speakers as time allows.
Note: Only the Chair and members of the Panel may question speakers during the open public hearing.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Marianne E. Baldwin
Vice President, Regulatory, Clinical, Quality
Cardima, Inc.
47266 Benicia Street
P.O. Box 14172
Fremont, CA 94538

Re: P020039
REVELATION® Tx Microcatheter with NavAblator Ablation System
Filed: September 23, 2002
Amended: November 6, 2002, January 16 and March 7, 2003

Dear Ms. Baldwin:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA). The Circulatory System Devices Panel, which also reviewed your PMA, recommended to CDRH at the May 29, 2003, panel meeting that the PMA be considered not approvable. We regret to inform you that CDRH concurs and has determined that your application is not approvable based on the requirements of 21 CFR 814.44(f), which also requires FDA, where practical, to identify measures necessary to make the PMA approvable. Accordingly, to place your PMA in approvable form, you must amend your PMA to include the following:

1. We believe that the clinical evidence provided in this PMA application does not demonstrate a reasonable assurance of safety or effectiveness as described in 21 CFR 860.7(d-e) respectively. Specifically, we note the following issues which need to be addressed with respect to the submission and analysis of clinical data submitted in this application:

    a. The clinical study lacked an accurate measurement of effectiveness endpoints, due to the following confounding factors:

        i. Failure to assure patient compliance with the measuring tool used to collect data to evaluate the effectiveness endpoint; and

        ii. Failure to clearly define a method to determine if symptomatic episodes reported by the patient represented discrete episodes of atrial fibrillation.

b. The clinical study lacked a consistently defined acute procedural endpoint that would allow assessment of effectiveness of the device system and provide a basis for developing instructions for use.

c. The clinical study lacked complete adherence to the investigational protocol by all investigators at all investigational sites, with respect to:

   i. performance of the same ablation procedure with the investigational device; and

   ii. initial attempted use of the investigational device system catheters only.

d. The clinical study results were potentially biased by changes to patient antiarrhythmic medications.

e. The clinical study did not contain careful characterization of the study population in terms of the pre-existing co-morbidities, such as sinus node function, which made it difficult to evaluate the effects of the ablation procedure on key patient parameters.

f. The lack of a control arm made the trial vulnerable to biases and artifacts, such as placebo effects.

We recommend that you schedule a meeting with us to discuss how these issues will be addressed in a future submission.

2. In Module 3 of the PMA submission, you provided a report of lesion comparison testing which was designed to demonstrate that the NavAblator™ creates lesions that were similar in depth and degree as legally marketed ablation catheters used in the clinical study. This bench testing did not include ample number of legally marketed (4 mm) radiofrequency ablation catheters. As previously outlined in an email set on May 6, 2003, please provide the test results analysis from your catheter comparison testing with the appropriate sample size, which demonstrate the equivalence of the lesions created by the subject device and legally marketed catheters used in the clinical study.

3. Please address the following with respect to the Customer Experience Reports described in P020039/A002, Volume 1, pages 37-38, Volume 2, pages 81-89, Table F43:

   a. This table documents several electrical and cable failures, as well as coagulum formation. Please provide a detailed explanation of how you plan to address or mitigate these failures in order to ensure appropriate catheter performance during actual use.

   b. This table documents several reports of the de-lamination of THV. The rationale to address this issue is insufficient because you have not provided a reasonable explanation on how you plan to ensure the manufacturability and quality assurance of

your catheters. Please provide a detailed explanation of how you plan to mitigate the de-lamination of THV in order to ensure the reproducibility and manufacturability of your catheters.

4. In Module 4 of the PMA submission, you provided incomplete documentation in order to support a 3 year shelf life for your devices. In the report, you indicate that aged samples failed tests and that tests should be repeated on samples having the corrective actions. However, no data were submitted on these samples. Please provide this documentation.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your PMA application can be completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided by 21 CFR 814.44(f), you may amend your PMA as requested above, withdraw the PMA, or consider this letter to be a denial of approval of the PMA under 21 CFR 814.45 and request administrative review. Any request for administrative review, either through a hearing or review by an independent advisory committee, under section 515(d)(4) and 515(g) of the Federal Food, Drug, and Cosmetic Act, must be submitted in the form of a petition for reconsideration under 21 CFR 10.33 and in accordance with the general administrative procedures under 21 CFR 10.20. Any petition for reconsideration must be submitted to the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1061, 5630 Fishers Lane, Rockville, Maryland 20852, within 30 days of your receipt of this letter. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the person may participate in the review, the time and place where the review will occur, and other details.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180-day period to (1) correct the above deficiency(ies), or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA number and will be subject to the requirements of 21 CFR 814.20.

You may amend the PMA to provide the above requested information (6 copies), voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information or request an extension.

The required copies of the amended PMA should include the FDA reference number to facilitate processing for this PMA and should be submitted to the following address:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this not approvable letter, please contact Cindy Demian, M.S. at (301) 443-8517, ext. 172.

Sincerely yours,

Daniel G. Schultz, M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

CLINICAL CONSULT

TO: CINDY DEMIAN

FROM: LESLEY EWING

FILE#: P020039/A6

SPONSOR: CARDIMA, INC.

DEVICE: REVELATION TX MICROCATHETER AND 4MM NAVABLATOR ABLATION CATHETERS

DATE: 20 MARCH 2004

CC: ELIAS MALLIS

Background of this submission:

This amendment to the PMA is sent to respond to the Not Approvable letter dated June 26, 2003.

Material reviewed for this memo:

Introductory letter, responses to deficiencies contained in the Not Approvable letter, material under tabs: Executive Summary, Clinical Protocol Summary, Results and Appendices E, F and G.

Review of data presented in this submission:

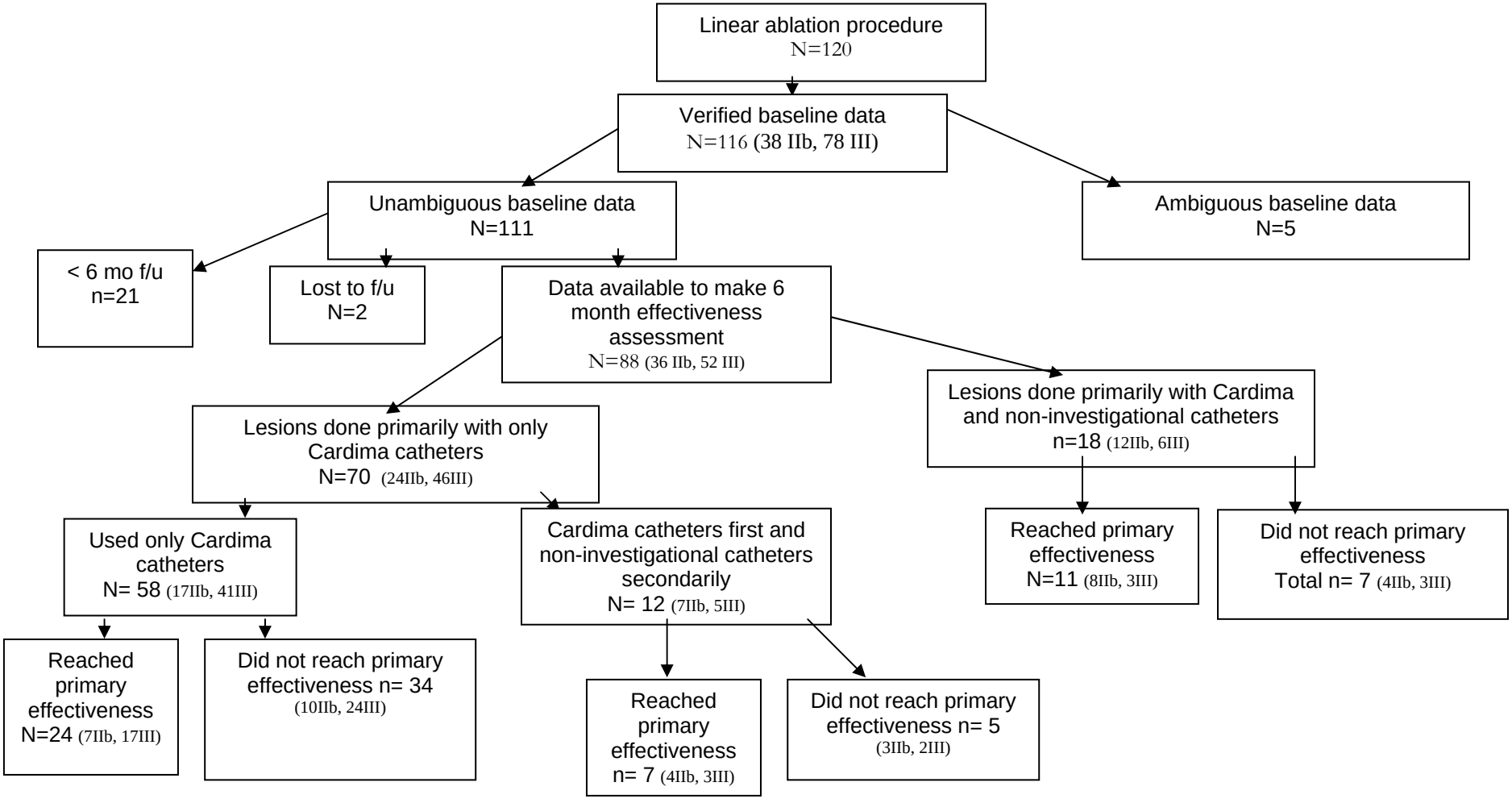
The original PMA submission (clinical module) submitted in September 2002 contained data on patients enrolled in phase IIB and phase III of the clinical trial. This amendment contains an analysis of only patients in phase III, which presumably is still ongoing. Phase III began with the introduction of the NavAblator (standard 4mm ablation catheter) to be used to create the linear lesion at the cavo-tricuspid isthmus. All patients in phase III were to have one of the investigational catheters used first to create linear lesions.

Diagrams of patient accountability are presented on the next two pages of this review memo.

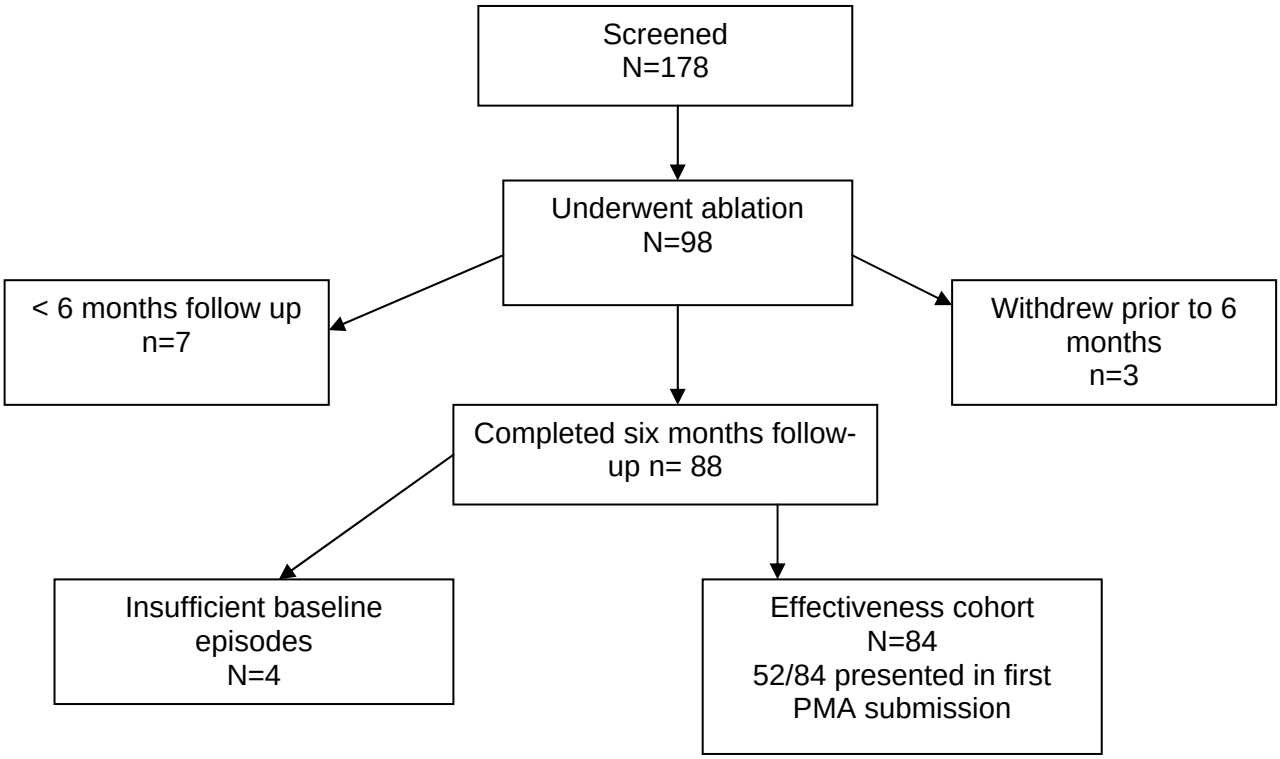
The sponsor now states that 47/84 patients or 56% reached the target level of decrease in symptomatic atrial fibrillation episodes. I believe that the denominator should include the 3 patients that withdrew prior to 6 months, and those patients should be considered failures in an ITT analysis. The sponsor has not provided any line data in this amendment. They have not provided any data on transtelephonic transmissions per patient, medications per patient or identification of which patients they consider successes and which they consider failures.

The sponsor has reanalyzed the trans-telephonic transmissions sent in at the six month time period and has adjusted their success rate downward while increasing the percent of patients that they say were compliant with the trans-telephonic transmissions. They have increased the number of patients with this compliance by increasing the amount of time they considered to be "six months" post ablation.

Patient accountability from original PMA



Patient accountability for current amendment



Sponsor's answers to deficiencies:

Compliance with trans-telephonic monitoring (TTM) (measuring tool used to collect data to evaluate the effectiveness endpoint):

The sponsor states that they now assess that 71% of subjects in phase III provided four or more transmission during the sixth month of follow-up and 82% had three or more transmission. They have not provided the line data to support this assertion. As stated above the sponsor has changed the time period called "the sixth month of follow-up" to allow for the study visit date flexibility allowed in the investigational protocol. It appears that they are now calling 151-210 days post ablation as the six month follow-up as opposed to the 151-180 days initially evaluated for the first PMA submission.

Accurate counting of episodes (each transmission a discrete episode?):

The effectiveness endpoint of this trial depends on each patient achieving either a 50% or 75% decrease in symptomatic episode numbers at six months post ablation compared to the baseline number. The accuracy of the measurement of episode numbers at each time period will determine

the ability of the study to determine effectiveness of the Revelation catheter. The effectiveness of the NavAblator catheter can be determined by the production of bi-directional conduction block (BDB) at the cavo-tricuspid isthmus.

The sponsor admits that there was no mechanism to determine if each transmission of atrial fibrillation represented one episode or if the patient transmitted multiple times during each episode. The sponsor states that 4.3% of transmitted AF episodes occurred within one hour of the previous episode at baseline and 1.9% at six months. The sponsor performed a sensitivity analysis to determine if the proportion of patients achieving the target level event reduction changed if episodes reported in close time proximity to each other were assumed to be one event instead of more than one event. They state that this analysis shows that potential over-reporting of episodes does not change the number of patients that achieved the correct amount of episode reduction.

The line data from which these analyses were based are not included in the submission.

Acute procedural endpoint:

The sponsor argues that there is no regulatory requirement that instructions for use be based on an acute procedural endpoint. The sponsor stated in the original PMA submission that "sufficient data to demonstrate either success or failure for the procedural endpoint are not available". When discussed at the May 29, 2004 Advisory Panel meeting the sponsor stated that the investigators looked at atrial electrograms and watched for a decrease in the electrograms. The sponsor does state that there is a clear procedural endpoint for the use of the NavAblator catheter.

Page 85 of 293, "While the design of the Revelation Tx catheter promotes the creation of lines of block in the atrium, measurement of atrial electrogram amplitude reductions does not guarantee that a line of block has been successfully created."

Because there was no clear procedural endpoint adhered to by the investigators, the FDA has no way to determine whether each investigator was performing the same or similar ablation lesions. Indeed from the procedural data provided by the sponsor, pages 77-79 of 293, there is evidence that each procedure varied widely from others. The mean procedure time was 218 minutes with SD of 11 minutes and range of 100 to 549 minutes. The mean fluoroscopy time was 43 minutes with SD of 42 minutes and range of 10 to 265 minutes. The FDA can not conclude that all the procedures were performed in the same way, that is, if the lesions were performed in the same or similar ways.

Adherence to the investigational protocol:

Performance of same lesions sets - in phase III the majority of patients did receive the same lesion sets. Some patients did not receive a cavo-tricuspid isthmus lesion if they had had the history of a prior ablation for atrial flutter.

Use of the investigational catheter first to perform lesions – The Revelation catheter was used to perform all the non isthmus linear lesions in phase III. In 4 procedures investigators used a non-investigational catheter for the initial application of RF energy to the tricuspid isthmus. These non-

protocol uses occurred at two sites and the sponsor states that they don't know why these two investigators chose to be non-compliant with the protocol.

Catheters used to ablated the isthmus in Phase III

Catheter	Frequency	%
NavAblator	51	57.3
NavAblator, then other	20	22.5
Revelation Tx	8	0
Revelation Tx, then NavAblator	3	3.4
Revelation Tx, then NavAblator, then other	3	3.4
Other	4	4.5
Total	**89**	**100**

Study results were potentially biased by changes to patient antiarrhythmic medications AAD:

The study protocol states that the effectiveness endpoint is a certain amount of decrease in the number of symptomatic episodes while "either maintained on the same anti-arrhythmic drug regimen or a reduced dosage". The sponsor has performed several analyses of AAD use in the patients of this study. They include a short description of an analysis performed by two physicians (one cardiologist and one electrophysiologist) of the AAD use in this study.

They conclude that because the patients were drug refractory at enrollment any AAD use would not have affected the reduction of episodes reported in the study.

This argument means that they do not believe the protocol definition of success needs to be adhered to. The number of patients that they report to be a success of the ablation procedure reflects this position.

Although it is possible that AADs change may not have altered the eventual number of symptomatic episodes, this argument ignores the fact that the treating physician felt a need to change or add AADs for that particular patient. If the patient was doing well why would they have needed additional AAD therapy? The study was designed that if the patient required an additional AAD or additional dosage of a baseline AAD then the ablation procedure had not achieved success.

Lack of careful characterization of pre-existing co-morbidities making it difficult to assess patient safety:

The sponsor provided a list of baseline information collected.

Lack of control arm made study vulnerable to bias and placebo effect:

The sponsor states that "the before-after design used in the Cardima investigations, though not containing a control arm, represents a type of external control (section 1.3.5). External controls are appropriate when the subject's condition is well-documented and the signs and symptoms are predictable."

The sponsor showed in the original PMA submission that the individual patient was not accurate in determining whether an episode of palpitations was really atrial fibrillation and therefore the

statement above does not apply to the subjective endpoint of this study or to the nature of paroxysmal atrial fibrillation.

The sponsor states that regression to the mean did not affect the data collected in this study. They base this conclusion on the fact that the patient population enrolled was not an extreme portion of the target patient population. They state that very few patients enrolled in the study could have had an exceptionally bad period of events, in terms of event numbers, in the baseline period because one month was required for baseline monitoring.

Procedural effectiveness of the NavAblator ablation catheter

The determination of effectiveness of the NavAblator catheter depended both on the chronic effectiveness endpoint of decrease in number of atrial fibrillation events and on the production of bi-directional conduction block (BDB) at the cavo-tricuspid isthmus. The production of BDB with radiofrequency energy has been accepted by the FDA as a surrogate endpoint for effectiveness. Objective performance criteria have been used to assess the percentage of patients having successful BDB with an ablation catheter to have market approval by the FDA.

Catheters used to ablate the tricuspid isthmus

Catheter	Frequency	%
NavAblator	51	57.3
NavAblator, then other	20	22.5
Revelation Tx	8	0
Revelation Tx, then NavAblator	3	3.4
Revelation Tx, then NavAblator, then other	3	3.4
Other	4	4.5
Total	**89**	**100**

Number of subjects in whom bidirectional conduction block was demonstrated or attempted by isthmus catheter used

	Demonstrated	Attempted
NavAblator	45	51
NavAblator, then other	15	20
Revelation Tx	4	8
Revelation Tx then NavAblator	3	3
Revelation Tx, NavAblator, then Other	3	3
Other	4	4

In phase III the NavAblator was used in 77/89 (87%) procedures in which there was isthmus ablation. Six patients had previous isthmus ablation. The NavAblator was the first catheter used in 71/89 (80%) procedures. The NavAblator (either alone or after use of the Revelation Tx) was successful in achieving BDB in 48/77 (62%). The point estimate of 62% does not reach the OPC.

Other analyses provided by the sponsor:

The sponsor provides an analysis of the QOL questionnaires completed by the patients. This information is difficult to impossible to evaluate without a concurrently selected control group or blinding of the treatment group.

The sponsor provides an analysis of the emergency visits and hospitalizations of the enrolled patients. This data is difficult to impossible to evaluate without a concurrently selected control group as a comparator.

The sponsor provides an analysis of pacemaker use in the patients in this study and discusses literature descriptions of pacemaker use in a patient population they state is similar. The analysis of pacemaker use or need for pacemaker implantation in this group is impossible without a concurrently identified patient group as comparators.

Conclusion:

The sponsor has not addressed most of the agency's concerns over this study. They have not provided evidence that the device system is safe or effective. They have provided evidence that the NavAblator is not effective.

Recommendation: The PMA amendment is not approvable.

Date March 25, 2004

From Mathematical Statistician (Heng Li) HFZ-542
Division of Biostatistics, OSB

Subject Statistical Review of PMA P020039/A6, Cardima, Inc.
REVELATION Tx Ablation System, (1/22/2004)

To Cindy Demian - HFZ-450
Division of Cardiovascular Devices, ODE

INTRODUCTION

The purpose of this PMA amendment (P020039/A6) is to address the questions and comments in the June 26, 2003 “not approvable” letter issued by FDA on Cardima’s REVELATION Tx Ablation System. In this reviewer’s opinion, all the comments and questions in the “not approvable” letter have not been adequately responded to. The inadequacy in the sponsor’s response falls mainly into three categories: 1) making statements without understanding the meaning of FDA’s questions and comments and/or certain terms appearing in them, 2) making unfounded claims, and 3) providing historical background where scientific justification is needed. The above categorization is only for the purpose of organizing the current review, and is not meant to be mutually exclusive and exhaustive. A problematic response from the sponsor may be considered as falling into more than one category, and different interpretations of a problematic response may assign it to different categories. Since in the current PMA amendment the results of the clinical study still appear not to have been obtained in a completely clinically indisputable way, this review does not comment on those results. Instead, it focuses on the sponsor’s response to FDA’s “not approvable” letter.

PROBLEMATIC RESPONSES TO FDA’S “NOT APPROVABLE” LETTER

1. **Misunderstood Questions and/or Terms.** Item 1f in the FDA’s “not approvable” letter states that “The lack of a control arm made the trial vulnerable to biases and artifacts, such as placebo effect.” In response, the sponsor stated that "Subjects in the study did not receive a placebo or a sham treatment, and therefore they cannot be subject to a placebo effect in the true sense of this phenomenon" (p.12). It seems that the above statement is based on a misunderstanding of the term "placebo effect". A common definition of 'placebo effect' of a treatment is the measurable, observable, or felt improvement in health not attributable to the treatment. Its existence does not require a placebo or sham treatment being actually administered.

   In the response to the same item, the sponsor cited one recent study in which Hawthorne effect was found to have no clinically significant influence (p.13). The

mentioning of Hawthorne effect may reflect the sponsor's misunderstanding either of this term or of FDA's comment. The original meaning of Hawthorne effect, that "the mere act of showing people that you are concerned about them usually spurs them to better job performance" has little relevance in the current context, and there is no implication in the FDA's comment that the sponsor is asked to address the issue of Hawthorne effect.

2. **Unfounded Claims.** The sponsor claimed that "Regression to the mean probably did not play an important role in the determination of device effectiveness" (p.12). However, little support has been provided for this claim. It is universally recognized that regression to the mean is a phenomenon associated with biological variation over time and measurement error, of which both are present in the study under consideration. When the criteria for selection to begin the intervention depend on the same variable that is used to assess the responses, regression to the mean will confound a straightforward comparison of the variable levels before and after the intervention. So the issue here is to quantify the regression-to-the-mean effect, and to do so we need longitudinal data not only on subjects who are selected, but also on subjects who are not selected. One cannot deny the importance of regression to the mean effect by just looking at the baseline values for patients selected for intervention, as the sponsor did. Of course there are additional complications in the current study with regard to regression to the mean, such as multiple screening of some patients.

   The sponsor claimed that "Due to selection criteria, study subjects were highly aware of their symptoms and frustrated with previous therapeutic maneuvers. They thus had little motivation to over- or under-report the occurrence of symptomatic episodes" (p.12). The above argument does not seem to be based on sound logic. Indeed, the frustration with previous therapeutic maneuvers may have made the patients eager to get into the study and therefore have motivated them to report more symptomatic episodes during the screening period. This same motivation of course couldn't have existed during the six-month follow-up period post ablation. It is such potentials for *differential* over- and under- reporting during the screening and follow-up periods that threatens the validity of study results, and therefore are of major concern.

   Regarding the compliance with rhythm strip recording, the sponsor claimed that "compliance was sufficient to allow valid conclusions about the effectiveness rate of the device" (p. 2). The sponsor has provided no evidence to support this claim. On the contrary, the sponsor provided evidence that by moving to the more compliant segment of the study the treatment success rate is lowered. This is evidence against an argument put forward in the sponsor's panel presentation that not reporting means no symptomatic episodes. So the data provided in this PMA amendment serve to confirm that compliance a more serious issue instead of a less serious issue.

   Regarding the ability of patients to report a single symptomatic episode as a single symptomatic episode (instead of multiple episodes), the sponsor conducted a sensitivity analysis in which the success rate is re-calculated with reported

symptomatic episodes less than one hour apart counted as a single episode. This sensitivity analysis does not address the possibility that the ability of patients to report a single symptomatic episode as a single symptomatic episode may improve over time, which is FDA's original concern.

3. **Scientific Justification vs. Historical Background.** In responding to several of FDA's questions and comments, the sponsor took a 'historical approach'. For example, in several places the sponsor cited documentation of a July 1998 Circulatory Panel Meeting, which may have been superceded by more recent guidance documents. The 'historical approach' may not be considered as adequate for some of the responses.

COMMENTS FOR THE SPONSOR

1. This PMA amendment seems to have provided additional evidence for the concern that compliance with rhythm strip recording is a serious problem, since it showed that by moving to a more compliant segment of the study the treatment success rate is lowered.. Therefore the claim that "compliance was sufficient to allow valid conclusions about the effectiveness rate of the device" (p. 2) seems to be unfounded.
2. The sensitivity analysis you provided with regard to the issue of discreteness of reported episodes of atrial fibrillation does not address the possibility that the ability of patients to report a single symptomatic episode as a single symptomatic episode may improve over time, which is FDA's original concern.
3. You claimed that "Due to selection criteria, study subjects were highly aware of their symptoms and frustrated with previous therapeutic maneuvers. They thus had little motivation to over- or under-report the occurrence of symptomatic episodes" (p.12). The above argument does not seem to be based on sound logic. Indeed, the frustration with previous therapeutic maneuvers may have made the patients eager to get into the study and therefore have motivated them to report more symptomatic episodes during the screening period to meet the threshold. This same motivation of course could not have existed during the six-month follow-up period post ablation. It is such potential tendencies for *differential* over- and under-reporting during the screening and follow-up periods that compromise the validity of study results, and therefore are of major concern.
4. You claimed that "Regression to the mean probably did not play an important role in the determination of device effectiveness" (p.12), without providing adequate supporting evidence. It is universally recognized that regression to the mean is a phenomenon associated with biological variation over time and measurement error, of which both are present in the study under consideration. When the criteria for selection to begin the intervention depend on the same variable that is used to assess the responses, regression to the mean will confound a straightforward comparison of the variable levels before and after the intervention. So the issue here is to quantify the regression-to-the-mean effect, and to do so we need longitudinal data not only on subjects who are selected, but also on subjects who are not selected. One cannot deny the importance of regression to the mean effect by just looking at the baseline values

for patients selected for intervention. In the current study, there are also additional complications with regard to regression to the mean, such as multiple screening of the same patient and differential over- and under-reporting.

5. You stated that "Subjects in the study did not receive a placebo or a sham treatment, and therefore they cannot be subject to a placebo effect in the true sense of this phenomenon" (p.12). It seems that the above statement is based on a misunderstanding of the term "placebo effect". A common definition of 'placebo effect' of a treatment is the measurable, observable, or felt improvement in health not attributable to the treatment. Its existence does not require a placebo or sham treatment being actually administered.
6. You cited one recent study in which Hawthorne effect was found to have no clinically significant influence (p.13). The mentioning of Hawthorne effect may reflect your misunderstanding either of this term or of FDA's comment. The original meaning of Hawthorne effect, that "the mere act of showing people that you are concerned about them usually spurs them to better job performance" has little relevance in the current context, and there is no implication in the FDA's comment that you are asked to address the issue of Hawthorne effect.
7. The issue of the usage of non-investigational devices in the clinical study seems not to have been completely resolved.

Heng Li, Ph.D.

cc: Bram Zuckerman, MD (HFZ-450)
Elias Mallis (HFZ-450)
Lilly Yue (HFZ-542)
BIMO (HFZ-310)
DCC (HFZ-401)
Medical Device File
Board File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

MAY 21 2004

Daniel Cher, MD
Medical Director
Cardima, Inc.
47266 Benicia Street
P.O. Box 14172
Fremont, CA 94538

Re: P020039
REVELATION® Tx Microcatheter with NavAblator Ablation System
Filed: September 23, 2002
Amended: November 6, 2002, January 16, March 7, October 22 and November 05, 2003, January 21 and March 8, 2004

Dear Dr. Cher:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA). We regret to inform you that CDRH has determined that your PMA is not approvable based on the requirements of 21 CFR 814.44(f), and, where practical, FDA must identify measures necessary to make the PMA approvable.

Specifically, your submission is not approvable because the clinical study design and results were inadequate to demonstrate a reasonable assurance of safety and effectiveness of the REVELATION® Tx Microcatheter with NavAblator Ablation System indicated for the treatment of drug refractory paroxysmal atrial fibrillation. While you have provided additional clinical information on 32 patients, the concerns identified in our June 26, 2003, not-approvable letter remain unresolved, as outlined in the deficiencies below.

While we believe that the safety and effectiveness information collected thus far provides some support for the safety and effectiveness of your device, the fundamental problems with the study design limit the conclusions that can be drawn from these data. Therefore, FDA believes that the least burdensome approach to demonstrate the safety and effectiveness of your device is to collect additional clinical data using a study design that addresses these fundamental problems. We strongly encourage you to meet with us to discuss how to most rapidly proceed with an optimal, least burdensome study design which addresses these key issues.

Accordingly, to place your PMA in approvable form, you must amend it to include the following:

Future Study Concerns

1. Based on the issues with the study design and results identified above, the lack of a control arm made the trial susceptible to biases and artifacts, such as placebo effects. One method to minimize the impact of these above factors on future clinical trials is to conduct a randomized controlled trial. A randomized controlled trial will improve your ability to make reliable conclusions regarding outcomes, and may address the outcome measurement issues identified in FDA's June 26, 2003, not-approvable letter. We continue to believe that a single-arm clinical study that is conducted in such a way as to avoid the issues outlined in a and b below and the issues identified in the June 26, 2003 not-approvable letter could result in adequate data to support a marketing application. You need to conduct a new clinical trial addressing all outstanding issues, including those described below:

    a. You have not adequately addressed Deficiency 1 (a-d, and f) of our June 26, 2003, not-approvable letter. The clinical study lacked an accurate measurement of effectiveness endpoints, due to the following confounding factors:

        i. The study failed to clearly define a method to determine if symptomatic episodes reported by the patient represented discrete episodes of atrial fibrillation. In your response, you indicated that there was no mechanism to determine if each transmission of atrial fibrillation represented one discrete episode or multiple transmissions of the same episode. Your sensitivity analysis demonstrated the potential for over-reporting of episodes and did not change the number of patients who achieved the correct amount of episode reduction. Further, the submission did not contain patient line data from which these analyses were based.

        ii. The study failed to assure patient compliance with the transtelephonic monitoring used to evaluate the effectiveness endpoint. Specifically, you did not provide patient line data to support your assertion that 71% of subjects in phase III provided four or more transmissions during the six month of follow-up and that 82% had three or more transmissions. To address the lack of compliance with the transtelephonic monitoring, you altered the time window for the six month follow-up visit. It now appears that 151 to 210 days post ablation is the six month follow-up window, while originally the six month follow-up window was 151 to 180 days.

        iii. The clinical study lacked a consistently-defined acute procedural endpoint that would allow assessment of effectiveness of the device and provide a basis for developing appropriate instructions for use. Because no clear procedural endpoint was adhered to by the investigators, FDA cannot determine whether each investigator performed the same or similar ablation lesions. Further, the procedural data, provided on pages 77-79 of 293, demonstrated that the procedure

times varied widely among study investigators. There were apparently further inconsistencies in use of the investigational device system catheters, i.e., the order in which the investigational catheters were used, the frequency of use of the investigational catheters, and use of non-investigational catheters.

iv. The clinical study results were potentially biased by changes to patient antiarrhythmic drugs (AADs). In your study protocol, you stated that the effectiveness endpoint is a decrease in the number of symptomatic episodes while "either maintained on the same anti-arrhythmic drug regimen or a reduced dosage." You conclude that because the patients were drug refractory at enrollment, any AAD use would not have affected the reduction of episodes reported in the study. The Circulatory Systems Devices Panel and FDA disagree with this conclusion, because it is inconsistent with the effectiveness endpoint previously defined in your protocol, and because changes in medications confound analysis of the effectiveness endpoint.

b. Effectiveness of the NavAblator catheter was based on the decrease in number of atrial fibrillation events and the ability to produce bidirectional conduction block (BDB) at the cavo-tricuspid isthmus. The production of BDB with radiofrequency energy has been accepted by the FDA as a surrogate endpoint for effectiveness. Typically, an objective performance criterion (OPC) of 90% (80% lower bound) of patients having successful BDB with an ablation catheter is achieved. The NavAblator (either alone or after use of the Revelation Tx) was successful in achieving BDB in 48/77 (62%). FDA does not believe that you have adequately explained how these results demonstrate the safety and effectiveness of the NavAblator catheter.

Sterility Concerns

2. You indicate that you plan to change your gamma sterilization process from a dose of 38 kGy to 25 kGy using the AAMI TIR: 2001 Sterilization of health care products - Radiation sterilization - Substantiation of 25 kGy as a sterilization dose - Method VDmax, dated October 29, 2001. Please provide a summary of the validation data and include a discussion of the following:

   a. the average bioburden for the entire product unit;

   b. whether the entire product unit is applicable to the four situations discussed in the TIR;

   c. how the selected product unit is representative of the batch and how it was selected randomly;

d. whether or not the sample item portion (SIP) represents the entire product unit or a portion of the product unit;

e. the adequacy of the SIP, e.g., how it represents the microbial challenge and the diverse elements of the product unit;

f. the basis for the SIP calculation, e.g., surface area, weight, length, etc.; and,

g. a summary of the data from your VD_{max} substantiation, e.g., bioburden estimate, selection of the verification dose, confirmation of the verification, substantiation and statistical verification of the 25 kGy dose.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your PMA application can be completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided by 21 CFR 814.44(f), you may amend your PMA as requested above, withdraw the PMA, or consider this letter to be a denial of approval of the PMA under 21 CFR 814.45 and request administrative review. Any request for administrative review, either through a hearing or review by an independent advisory committee, under section 515(d)(4) and 515(g) of the Federal Food, Drug, and Cosmetic Act, must be submitted in the form of a petition for reconsideration under 21 CFR 10.33 and in accordance with the general administrative procedures under 21 CFR 10.20. Any petition for reconsideration must be submitted to the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1061, 5630 Fishers Lane, Rockville, Maryland 20852, within 30 days of your receipt of this letter. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the person may participate in the review, the time and place where the review will occur, and other details.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA number and will be subject to the requirements of 21 CFR 814.20.

You may amend the PMA to provide the above requested information (6 copies), voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information or request an extension.

The required copies of the amended PMA should include the FDA reference number to facilitate processing for this PMA and should be submitted to the following address:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this not approvable letter, please contact Cindy Demian, MSBE at (301) 443-8517.

Sincerely yours,

Donna-Bea Tillman, Ph. D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

CARDIMA®

P020039/A6
C1

January 20, 2004

Daniel G. Schultz, M.D.
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850

RE: PMA # P020039/A006

Dear Dr. Schultz:

FDA/CDRH/ODE/PMO
2003 JAN 1 P 3: 37
RECEIVED

In response to your June 26, 2003 letter, Cardima is submitting this amendment to its PMA to provide the requested information. The amendment consists of the attached document, titled Amendment Volume 12, and this letter. The PMA as amended demonstrates that the REVELATION® Tx Microcatheter Ablation System is safe and effective for the treatment of symptomatic paroxysmal atrial fibrillation (AF).

In preparing our responses to your letter, Cardima has taken the following steps in analyzing the data from its clinical studies:

1. The amendment focuses primarily on subjects enrolled in the Phase III trial. Patients from the Phase IIB trial are no longer included in the primary analyses.
2. The Phase III trial has continued after the original submission of the PMA on September 19, 2002. An additional 36 patients have undergone ablation, and the total number of Phase III subjects in the primary effectiveness analysis is 84, meeting the agreed-upon target sample of 80 patients.
3. We have conducted additional analyses of the data to respond to your questions concerning subject compliance, determination of whether symptomatic episodes reported by subjects were discrete, adherence to the protocol on the part of investigators with respect to lesion sets and the use of catheters other than the investigational catheter to ablate the isthmus, and changes to patients' antiarrhythmic medications. The methods by which these analyses were conducted and the results of these analyses are discussed in this letter and presented in full in the amendment.
4. The amendment also responds to the questions two through four of your letter, which concern manufacturing and shelf-life.

47266 Benicia Street P.O. Box 14172 Fremont, CA 94538-7330 Phone 510.354.0300 Fax 510.657.4476 www.cardima.com

To date, 98 patients have undergone ablation with REVELATION® Tx in the Phase III clinical trial. Of these, procedure-related data have been verified in 93 patients (the "procedure cohort") and 88 have reached the six-month endpoint (with 84 forming the "effectiveness cohort"). Long-term follow-up in the Phase III trial was excellent with no loss to follow-up. Of the 84, 49 subjects (58%) achieved the target-level decreases in monthly symptomatic AF episode counts from baseline to six months of follow-up to be considered successes. Forty-seven subjects (56%) had target-level reductions in symptomatic AF episode counts at six months not attributable to AV node ablations, pacemaker placements or AAD changes ("clinical (patient) success"). Note that only two subjects underwent a second ablation procedure. The serious adverse event rate during the study procedure was 4.2% events in 95 patients (4.2%).

We look forward to discussing this new information with the Agency.

Sincerely,

Daniel Cher MD

Daniel Cher, MD
Medical Director

Cc: Cindy Demian, MS
Elias Mallis, Branch Chief, Cardiovascular Devices

47266 Benicia Street P.O. Box 14172 Fremont, CA 94538-7330 Phone 510.354.0300 Fax 510.657.4476 www.cardima.com

Background. In September 2002, Cardima filed its PMAA with the submission of the fifth module, the clinical summary, which summarized clinical experience with the REVELATION® Tx catheter. On May 29, 2003, Cardima presented these findings at a Circulatory Systems Advisory Panel meeting. In a letter dated June 26, 2003, the Agency stated that it found the application "not approvable" and provided specific questions and comments which it stated must be addressed to make the PMA approvable.

Below, each of the Agency's concerns regarding the study is addressed. The Agency's questions are highlighted in *italic* font. Our responses are in regular font.

1a. "The clinical study lacked an accurate measurement of effectiveness endpoints, due to the following confounding factors:

i. Failure to assure patient compliance with the measuring tool used to collect data to evaluate the effectiveness endpoint.

Overall compliance with recording and transmitting event monitor rhythm strips in the Phase III trial was adequate. As detailed below, 71% of subjects in Phase III provided four or more transmissions during the sixth month of follow-up, and 82% provided three or more. In addition, compliance with quality of life outcomes assessed at the six-month study visit was excellent. These results indicate that subject compliance with the measuring tool used to collect data to evaluate the effectiveness endpoint was effectively assured. The measuring tool itself, cardiac event monitoring with event monitors, was and continues to be the only available measure of symptomatic AF episodes and was appropriate given the stated indication for the device. Combined with the study's adequate compliance rate, the measurement of effectiveness endpoints in the Phase III study can be considered an accurate representation of the underlying effect of the device.

As detailed in the PMA amendment, a more accurate approach to analysis has been utilized to account for study visit date flexibility allowed in the Protocol. The approach previously used to evaluate rhythm strip recordings, while reasonable, did not take account of protocol-allowed variation in the date of the six month visit. The six-month study visit could, per protocol, occur at 180 days plus or minus 30 days (i.e., in the range of 151 – 210 days); however, only rhythm strips from days 151 – 180 were utilized in assessing compliance and episode counts, no matter when the six month visit actually took place. Thus, transmissions which were in fact within the 30-day, six-month monitoring period may have been excluded from analysis. (Note that the subject's 30-day, six-month monitoring period, whose start date was not captured in case report forms, may not have been the actual 30 days prior to the six-month study visit.) We therefore used 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. While this approach had the effect of better assessing compliance (since it captured more transmissions), it also resulted in lowering of the reported treatment success rate (since some of the transmissions were episodes of symptomatic AF). Using this approach to determine compliance rates in Phase III at both three and six months, 74% and 71% of

3

subjects provided four or more transmissions during the third and six months, respectively, and 85% and 82% of subjects provided three or more transmissions during the third and six months, respectively. (Further analysis of compliance is provided in the attached PMA amendment.) Compliance with rhythm strip recording in Phase III was substantially better than that reported in the PMA for the pooled Phase IIB and III datasets; compliance was sufficient to allow valid conclusions about the effectiveness rate of the device.

ii. Failure to clearly define a method to determine if symptomatic episodes reported by the patient represented discrete episodes of atrial fibrillation"

The focus of the Cardima clinical investigations was on the frequency of episodes of symptomatic AF experienced by subjects with paroxysmal AF, not AF burden (the proportion of time spent in AF, independent of symptoms). The protocol therefore appropriately relied solely on subjects to determine when episodes both started and stopped; this practice is consistent with all studies in the published medical literature of AF ablation.

In theory, the measurement tool used to assess the occurrence of symptoms, the cardiac event monitor, could also have been used to document the end of an episode, proving its "discreteness;" however, this would have imposed a substantial burden on subjects, more than doubling the monitoring effort, and would have measured cardiac activity beyond the scope of this study and the indication for this device (symptomatic AF).

In theory, a subject in our study could have recorded multiple rhythm strips, denoting the occurrence of multiple symptomatic "episodes," during a single underlying "run" of AF. Such an occurrence could, if it happened differently between follow-up and baseline (for which there is no evidence), have resulted in a biased assessment of effect size.

In our study, a very small proportion of symptomatic AF episodes occurred within one hour of the previous episode: 4.3% at baseline and 1.9% at six months of follow-up. (As expected, due simply to a higher episode density at baseline than follow-up, the likelihood of reporting of an episode soon after a previous episode was larger at baseline than at follow-up.) Since the vast majority of episodes were separated by more than one hour and paroxysms of AF can occur within minutes of each other, duplicate recordings of the same "run" of AF was unlikely. In addition, a sensitivity analysis was performed, in which the proportion of patients achieving the target-level decrease in symptomatic AF episode count at six months was calculated after assuming that an episode reported "soon after" a previous episode might, due to close proximity, represent duplicate reporting of the same underlying run of AF. This sensitivity analysis showed (see Table 1) that the potential effect of the proposed duplicate recording on the overall success rate would, if it had actually occurred, have been negligible. Further details are provided in the attached PMA amendment. The clinical study used an appropriate method to measure the selected effectiveness endpoint for the device's proposed indication that was not biased by the potential for duplicate recording of episodes.

Table 1. Effect of "overreporting" on six-month success rates.

Minimum time between distinct episodes (hour)	Success Rate		
	Success	N	(%)
0 (baseline)	47	84	56.0
1	47	84	56.0
6	46	80	57.5
12	46	80	57.5
24	45	80	56.3

Assumes 7 non compliant patients are failures but would not have been affected by alternative definitions for episode counts. N decreased by four since elimination of the second episode at baseline would have disqualified these patients.

b. "The clinical study lacked a consistently defined acute procedural endpoint that would allow assessment of effectiveness of the device system and provide a basis for developing instructions for use."

There is no regulatory requirement that instructions for use be based on an acute procedural endpoint. According to the Agency's own Advisory Panel meeting of July 1998, such an endpoint for clinical trials of AF ablation does not exist. It is arguable that even in the current era, with marked advances in electrophysiologic imaging technologies, such an endpoint does not exist for linear lesions in the right atrium.

Nonetheless, throughout the study, the Protocol specified a well-defined acute procedural endpoint (atrial electrogram amplitude reduction), and this was measured in 83 of 95 (78%) of subjects. An additional, well-defined endpoint for isthmus ablation (bidirectional conduction block) was documented in all subjects undergoing this part of the procedure. The observation of a decrease in atrial electrogram amplitudes, combined with the study's pre-specified ablation protocol and other information about how to use the device, provides ample basis for development of instructions for use. Further discussion is provided below.

To our knowledge, there is no regulatory requirement for an acute procedural endpoint to develop instructions for use. Moreover, the lack of such an endpoint in AF ablation does not prevent development of instructions for use. As shown in our study, the application of the Protocol's specific recommendations for ablation parameters to create lesions (60 seconds, 35 watts, 55° C and 200 ohms maximum impedance) resulted in both substantial reductions in atrial electrogram amplitudes and successful clinical outcomes at three and six months of follow-up. The basis for developing instructions for use can be found in the fundamentals of the study protocol.

5

Acute procedural endpoints are common in other cardiac interventions for arrhythmias. For example, the ventricular tachycardia guidelines developed by the Agency[a] discuss the acute non-inducibility of clinically relevant VT morphologies as a procedural endpoint. (The July 1998 Panel on AF trials rejected non-inducibility of AF as an outcome.) The ablation target for non-AF supraventricular arrhythmias is often a single myocardial focus of activity; ablation of the focus results in non-inducibility or absence of electrical activity at the target, forming a reasonable acute procedural endpoint.

In contrast, there is no universally accepted acute procedural endpoint in AF ablation. In pulmonary vein (PV) isolation, which was not the target of the current investigation, the stated goal is to isolate potentially triggering electrical activity in the pulmonary veins through the creation of lesions that surround individual pulmonary veins or groups of veins. Both entrance and/or exit block, typically demonstrated with a "lasso" catheter, have been suggested as acute procedural endpoints for such lesions; even for PV isolation, some investigators continue to use decreases in PV amplitudes, since whether complete PV isolation is required for clinical success is not universally accepted. Exit or entrance block are not relevant outcomes for the creation of linear lesions in the right atrium. When creating linear lesion in the right atrium (and, it could be argued, in the creation of roof line and/or PV-to-mitral annulus lesions often created in left atrial ablations), the goal is substrate modification through the creation of lines of block; theoretically, such lines reduce AF by dispersing areas of refractoriness in the atrium to prevent AF sustenance. To date, there is no universally accepted acute procedural endpoint known to have clinical significance for procedures aimed primarily at the creation of linear lesions in the atria. This is because it remains unknown whether such lines need to block conduction completely to be clinically effective. The substantial differences in the proposed underlying mechanisms of action for these three different types of lesions (focal, lines for isolation and lines for substrate modification) are important when considering appropriate acute procedural endpoints.

In 1998, when the Agency's Advisory Panel on Atrial Fibrillation Ablations considered the issue, no acute procedural endpoint was proposed; rather, panel members suggested focusing on long-term outcomes. The situation had not changed when the Phase III trial was initiated in 2000. As discussed above, for procedures aimed primarily at substrate modification, no universally accepted endpoint exists even today.

For the linear ablation portion of the procedure, a reduction of atrial electrogram amplitudes from before to after ablation was selected as an acute procedural endpoint in the REVELATION® Tx clinical trials. This endpoint was selected due to its similarity with established clinical endpoints in the ablation of focal arrhythmias such as paroxysmal supraventricular tachycardias, the ablated tissue shows little or no electrical activity. At the time of trial design the endpoint was reasonable and no other endpoint was routinely in use; this endpoint continues to be used by some researchers, even in left-atrial ablations. In contrast to focal ablations, however, since this measurement was not known to have important clinical implications in AF ablation, no specific cutoff was selected to indicate that a particular acute procedural endpoint had been reached. The

[a] http://www.fda.gov/cdrh/ode/tachyabl.pdf

6

protocol noted ablation was to continue until the observation of a reduction in atrial electrogram amplitudes. As detailed in the attached PMA amendment, paired before-after measurements showed an average 56% reduction in atrial electrogram amplitudes, consistent with the study procedure having accomplished the target ablation.

For isthmus ablation, bidirectional conduction block (BDC) was selected as an acute procedural endpoint. Whether BDC was achieved was documented in all subjects in whom isthmus ablation was attempted. Note that in patients undergoing atrial flutter ablation, BDC is a physiologically relevant endpoint that is likely to predict flutter recurrence. Isthmus ablation is generally believed to reduce the occurrence of atrial flutter in subjects undergoing AF ablation; whether it impacts the occurrence of symptomatic AF is not known. As detailed in the attached PMA amendment, analysis of results from our clinical study did not show that subjects who had completed isthmus ablations (via demonstration of BDC) were more likely to show target-level reductions in symptomatic AF episodes.

c. "The clinical study lacked complete adherence to the investigational protocol by all investigators at all investigational sites, with respect to:

i. performance of the same ablation procedure with the investigational device; and

ii. initial attempted use of the investigational device system catheters only"

Through standard data query practices in place at Cardima, the performance of all ablation procedures in which the target lesion set was not used was reviewed with investigators; this review showed that all subjects received target lesion sets recommended in the protocol. Regarding initial use of investigational catheters, REVELATION® Tx was used to create linear lesions in all study subjects; initial use of study catheters to ablate the isthmus line occurred in 95% of all procedures. A detailed discussion is provided below.

It appears that the first concern relates to performance of the same lesion set across study subjects. Note that lesion sets recommended in the study protocol changed somewhat during Phase III. In Phase IIB and the initial Phase III protocol, the anterior "D" lesion was optional. Early in Phase III one patient experienced sinus block, which the investigator attributed to SA node isolation. The Agency was notified in September 2000 that this lesion was no longer recommended, investigators were notified, and the revised Protocol (August 2001) reflects this. As reviewed below, no subsequent Phase III subject received an anterior lesion.

In the PMA submission, the statistical summary of reported lesion sets indicated some variation in choice of lesion lines. This variation was probably due to several reasons: 1) the anterior line was optional in Phase IIB and early in Phase III, 2) several subjects had previous RF ablation of the isthmus for atrial flutter and the Protocol did not require retreatment of the isthmus line (such patients would have appropriately undergone an

7

"AB" lesion set), and 3) case report forms may have had some incomplete or inaccurate entries. These are reviewed below.

- In the prior PMA submission, seven subjects (five in Phase II, two in Phase III) were reported to have undergone only lesions A and B. All of these patients had previous isthmus ablation for atrial flutter, and the protocol did not require retreatment of the isthmus line. In some of these patients, bidirectional conduction block at the isthmus line was verified. Four newly reported Phase III patients included in the attached PMA amendment also underwent only lesions A and B for the same reason.

- In the prior PMA submission, ten other subjects (two in Phase II and eight in Phase III) were reported to have undergone lesions that were not part of the recommended ABC or ABCD lesion sets. All but two were previously reported to have undergone three lesions. As part of our normal data quality management process, study sites were asked for 1) clarification and source documents regarding lesion sets performed, and 2) review of source documents with study investigators. In written responses from study sites, all ten subjects were noted by study investigators to have undergone the three target lesion sets (ABC). One investigator (site 16), who had treated seven of the ten patients in question, informed us that he had he has never performed an anterior lesion.

After clarification of lesion sets with study sites, it was found that all lesion sets actually performed consisted entirely of target sets. In all, six Phase III procedures involved only lateral and septal lines; all six had undergone isthmus ablation prior to study enrollment. One Phase III patient had a second procedure in which the isthmus line only was re-ablated. In the remaining 88 procedures, lines A, B and C were created, consistent with the recommended lesion set.

The study Protocol had different recommendations for catheter use for ablating the isthmus line between study Phases. In the Phase IIB Protocol, isthmus ablation was to be attempted using the REVELATION® Tx catheter, and, if bidirectional conduction block could not be achieved, according to "standard institutional procedures." In Phase IIB, REVELATION® Tx was used initially in 35 of the 36 procedures (97%) in which an isthmus block was attempted (Table 2). The one procedure in which a non-study catheter was used represented a second procedure; in the subject's initial procedure, REVELATION® Tx was used to ablate the isthmus.

Table 2. Catheters used to ablate the isthmus line in Phase IIB.

Catheter(s) Used	Frequency	%
REVELATION® Tx	15	41.7
REVELATION® Tx, then other	20	55.6
Other	1	2.8
Total	36	100.0

8

In April 2000, at the time of submission of the Phase III Protocol, the Agency advised Cardima that it must specify one RF ablation catheter alternative for the isthmus line when REVELATION® Tx could not achieve the desired result. At that time, isthmus ablation had already been reported by multiple investigators to be safe and effective to treat atrial flutter; however, none of the catheters commonly used in these procedures were approved or cleared in the US for this specific indication. Cardima therefore developed NAVABLATOR®, a standard[b] 4-mm hot-tip catheter, which was deemed to be the alternative catheter (alternative to REVELATION® Tx) to ablate the isthmus line.

Table 3 shows the number and frequency of catheters used to ablate the isthmus line in Phase III. In only four cases (4.5%) did investigators use a non-study catheter in their initial attempt to ablate the isthmus line (see attached PMA amendment for specifics on catheters chosen). This occurred at two sites only. It is not known why these two investigators chose to use other catheters first. Possible reasons include: 1) the decreased radius of curvature of NAVABLATOR® compared to other devices, resulting in insufficient predicted "reach" of the catheter into the right ventricle, or 2) not using a flutter sheath, a guiding catheter than can be used to extend the reach of NAVABLATOR®.

Table 3. Catheters used to ablate the isthmus line in Phase III.

Catheter(s) Used	Frequency	%
NAVABLATOR®	51	57.3
NAVABLATOR®, then other	20	22.5
REVELATION® TX	8	9.0
REVELATION® TX, then NAVABLATOR®	3	3.4
REVELATION® TX, then NAVABLATOR®, then other	3	3.4
Other	4	4.5
Total	89	100.0

In six procedures, isthmus ablation was not attempted since it had been performed prior to study enrollment.

Isthmus ablation was added to the study Protocol in an attempt to prevent the occurrence of atrial flutter after linear AF ablation. Whether isthmus ablation is important for AF ablation is not clear. Subsequent analyses have not shown that the choice of isthmus catheters used was significantly related to six-month success rates.

In summary, clarification of lesion sets performed showed that investigator adhered to the study protocol with respect to performance of the same ablation procedure with the investigational device. In addition, initial use of non-investigational catheters was kept to a minimum in all study phases.

[b] As shown in our *in vitro* catheter comparison (see Appendix A of attached PMA amendment), when accounting for the fact that NAVABLATOR® is slightly larger (8F) than the other catheters used in the clinical study (7F), our catheter produces lesions of exactly the expected size.

9

d. "The clinical study results were potentially biased by changes to patient antiarrhythmic medications."

As a result of recruitment criteria, all study subjects had drug-refractory, symptomatic AF. While changes to antiarrhythmic drug (AAD) regimens did occur during the study, the impact of those changes was potentially overestimated due to: 1) consideration of changes among patients who did not achieve target-level reductions in symptomatic AF episodes, 2) incomplete analysis of the timing of AAD change vs. episode count changes, and 3) incomplete consideration of the negligible potential impact of new AADs in subjects with drug-refractory AF. To aid in the interpretation of AAD changes, a literature-based classification system was used and several alternatives to analysis were evaluated. Despite AAD changes in the clinical investigation, the observed effect of catheter ablation on symptomatic paroxysmal AF remained clinically important. A brief discussion of AAD changes, and their interpretation, is provided below with a fuller discussion in the attached PMA amendment.

From the outset, it should be acknowledged that consideration of AAD changes in subjects who did not show target-level reductions in symptomatic AF is not relevant to the clinical success outcome of the clinical investigation. Subjects who did not achieve target-level decreases were not, independent of AAD changes, considered to have any success outcome in the clinical investigation.

To aid in discussion of AAD changes, a literature review was performed, which focused on the effectiveness of AADs to reduce episodes of symptomatic AF. Details of the review are provided in the attached PMA amendment. It was noted that no guidelines or recommendations existed for the interpretation of AAD changes, and AAD changes have been handled variously in the published literature. Most published studies of AADs have focused on time to recurrence rather than the number of symptomatic episodes, and have typically not enrolled subjects with drug-refractory AF, limiting the application of such studies to the current investigation.

Table 4 shows the proposed approach for discussing AAD changes occurring in the current investigation. "Decrease" and "increase" represent changes that are fairly easy to determine, based on drug dosages. Addition of rate-control drugs was included as a separate category, since this maneuver was considered to be unlikely, by itself, to reduce the occurrence of symptomatic AF in our study subjects. Subjects who started an AAD to which they were previously refractory were also classified separately, in conjunction with methods used in many published study reports. Finally, patients who were started on a new AAD were separately identified. In all cases, the timing of the AAD regimen change with respect to episode count reductions was evaluated; target-level reductions in episode counts occurring prior to the new AAD or dose increase were considered to be attributable to catheter ablation.

In the Phase III study, three subjects had dose increases in AAD regimens; all three had target-level decreases in episode counts at three months prior to the dose increase; these subjects were therefore considered catheter ablation successes.

In the Phase III study, 12 subjects started new AADs; two started amiodarone, six started flecainide, two started propafenone, one started disopyramide, and one started dofetilide. Of these 12, one (III-1009) had a target-level decrease in symptomatic AF episode count prior to beginning amiodarone near the sixth month and was considered a clinical success. Whether the remaining 11 patients had changes attributable to catheter ablation or the new AAD depends on one's assumptions regarding AAD effectiveness to reduce episode counts by more than 50% in subjects with AAD-refractory AF. (The published medical literature provided no evidence to support a reduction of 50% or more necessary to be considered a clinical success.) Three approaches to analysis that take into account these assumptions were proposed (Table 5). These approaches allow an organized discussion of the effect of AAD changes on interpretation of the study's results. Even with the most pessimistic assumptions, the success rate of right-atrial catheter RF ablation remained clinically important.

Table 4. Proposed classification of AAD changes in patients with target reduction in counts of symptomatic AF.

Classification	Detail	Example	Interpretation*
Decrease	Off AADs		Success
	Decrease in dose of AADs	Propafenone 100 mg BID → 100 mg QD	Success
Increase	Increase in dose of AADs without addition of other agents	Amiodarone 200 mg QD → 400 mg QD	Not success
Rate Control Drug Only	Increase in dose or change in type of rate-control agents only	Add metoprolol	Success
New AAD	Starting an agent to which subject not previously exposed	Add amiodarone at 3 months	Depends on assumptions regarding AAD effectiveness in drug-refractory AF
Use Previous	Start AAD to which previously refractory	Subject refractory to flecainide but not on it at baseline. Restart flecainide in follow-up.	Success

*All interpretations depend on timing of AAD change with respect to episode reduction

11

Table 5. Approaches for interpreting new AADs and impact on analysis.

Approach	Assumption	Success Rate[a]
1. Drug-refractory	Patients are drug-refractory. The new AAD was unlikely to cause a clinically substantial decrease in episode count by itself. Attribute the episode reduction to catheter RF ablation.	47/84 (56%)
2. Not drug refractory	Despite non-response to 2 or more drugs prior to enrollment, patients are not really drug-refractory. The new AAD caused most of the target-level reduction in symptomatic episode counts. Attribute the decrease to the new AAD.	36/84 (43%)
3. Uninterpretable	Effect confounded. One cannot tell whether effect due to AAD or linear catheter ablation. Exclude such patients as "unevaluable."	36/73 (49%)

Notes: a) Excludes from numerator two patients who achieved target-level symptomatic AF episode reduction but had AV node ablation plus pacemakers placed within first six months of follow-up; includes three patients as successes who had increases in AAD regimens that were preceded by target-level decreases in symptomatic AF episodes. See PMA amendment for full discussion.

Finally, simultaneous with our review and preparation of the above analysis, a substudy was performed in which two independent, practicing cardiologists not involved with Cardima were asked to independently develop their own categorization systems for changes to AAD regimens and apply their system to drug changes occurring in all study subjects. This study is attached as Appendix C to the PMA amendment. The main finding of this study was that these cardiologists noted that in some cases addition of a new AAD did not necessarily represent an AAD increase and sometimes was a decrease.

In summary, a simple, literature-based approach was used to classify Protocol-allowed AAD changes occurring during the trial. This specific approach allows an organized discussion of the study's results. Even with the most pessimistic assumptions, the success rate of right-atrial catheter RF ablation remained clinically important.

e. "The clinical study did not contain careful characterization of the study population in terms of the pre-existing co-morbidities, such as sinus node function, which made it difficult to evaluate the effects of the ablation procedure on key patient parameters."

Extensive demographic and clinical baseline information was collected for the trial's study population (Table 6) and this information is reported in the PMA amendment. The characterization provided ample description of the study population such that a physician reading the trial can determine whether a patient whose treatment he or she is considering is similar to subjects treated in our investigation. In addition, the effect of ablation on key cardiac conduction parameters was assessed after ablation, and follow-up EKGs were

12

obtained. Since catheter ablation was not expected to affect sinus node function, this parameter was not specifically assessed.

The study was designed solely to assess the effects of ablation on the number of episodes of symptomatic AF, and the study successfully allows assessment of the safety and efficacy of the device in reducing AF in patients with a variety of pre-existing comorbidities. The study was not designed to support subgroup analyses.

Table 6. Baseline information collected on study patients in REVELATION® Tx investigations.

1. Demographic variables (age, sex, etc.)
2. AF duration
3. AF symptoms, both subjective and via AFSS
4. Previous interventions for AF, including previous RF ablations
5. Medications used to treat AF at baseline
6. Medications to which refractory
7. Baseline monitoring of symptoms with cardiac event monitors
8. Presence/absence of bleeding disorders
9. Presence/absence of diagnosed heart disease, including structural heart disease (valvular disease, aneurysm, LVH)
10. Documentation of heart disease via pre-procedure transesophageal echocardiogram (TEE)
11. Pre-procedure EKG with detailed analysis
12. Follow-up EKGs
13. Pre-procedure stress test
14. Physical examination parameters (weight, heart rate, blood pressure, cardiovascular findings) before and after procedure
15. Presence/absence of other comorbidities (respiratory, endocrine, renal, neurological, hematopoietic, lymphatic, musculoskeletal, gastrointestinal, psychological, immunologic illness)
16. Pre-ablation standard mapping procedure, according to the investigator's routine practice
17. AH and HV intervals before and after ablation

f. "The lack of a control arm made the trial vulnerable to biases and artifacts, such as placebo effects."

According to the ICH Guidance for Industry document on choice of control group in clinical trials (May 2001), the before-after design used in the Cardima investigations, though not containing a control arm, represents a type of external control (section 1.3.5). External controls are appropriate when the subject's condition is well-documented and the signs and symptoms are predictable (21 CFR § 860.7(f)(1)(iv)(d), the ICH Guidance, Section 2.5.1), which was the case for enrolled subjects.

FDA's Guidance on the Least Burdensome Provisions state that valid scientific evidence does not necessarily require conducting a randomized trial with a control arm (p. 9) and the before-after study design has been found satisfactory in other device trials (p. 11). Furthermore, the provisions recognize a design in which "patients serve as their own baseline control" (p. 11), which is valid in situations in which there is no satisfactory intervention for the disease being studied; this was certainly the case in Cardima's study since all subjects had AF refractory to AADs and other invasive AF procedures were not considered standard of care.

Finally, the before-after study design used in our trial was in accordance with the recommendations from the Agency's Advisory Panel Meeting of July 1998 for AF trials (see p. 111 of transcript).

The similarity of design of our study to most published studies attests to its widespread application in studies of catheter ablation for AF and allows a reasonable comparison of results across studies. Sham ablation would not have been acceptable to either patients or physicians, and RF ablation trials with sham arms have not been performed to date. Most published trials of AF ablation did not use control arms. Continued pharmacotherapy as a concurrent control arm would have severely limited enrollment rates.

Cardima took a number of steps to minimize the impact of potential biases and artifacts, and the study results were, accordingly, interpretable. First, the primary outcome was measured with event monitors, not retrospective self-report, as done in most studies. Second, the Protocol required a substantial baseline monitoring period, using the same reporting protocol as after the RF ablation procedure. Use of a time-invariant protocol for recording episodes should help to prevent reporting biases.

Due to selection criteria, study subjects were highly aware of their symptoms and frustrated with previous therapeutic maneuvers. They thus had little motivation to over- or under-report the occurrence of symptomatic episodes.

Subjects in the study did not receive a placebo or sham treatment, and therefore they cannot be subject to a placebo effect in the true sense of this phenomenon.

Regression to the mean probably did not play an important role in determination of device effectiveness. This phenomenon occurs when an extreme portion of a target population is sampled. In theory, if subjects were enrolled after unusually "bad" months, with more than the usual number of symptomatic episodes, measurements occurring in subsequent months would be lower, on average, due to chance alone. This would only be the case if the study population's underlying mean episode frequency was close to the threshold value used for qualification. However, the mean baseline number of monthly episodes (9) was far above the cutoff value (3) and 69% of subjects had five or more episodes at baseline, suggesting that very few subjects who underwent ablation qualified as a result of chance. The one-month of baseline monitoring for qualification was believed by investigators to be of sufficient duration to ensure a representative patient experience both for study entry and for comparison to follow-up experience. Thus, it is not likely that regression to the mean is a source of bias in this trial.

The Hawthorne effect, originally described in research findings from a Chicago-area utility company in the 1930s, describes a change (in this case improvement) in an outcome thought to result simply from closely observing the process producing the outcome. The degree to which the Hawthorne effect affects clinical studies has not been generally described. In the current study, the Hawthorne effect would have to be opposite at baseline vs. follow-up in order to introduce bias. Subjects in our study had no motivation to over- or under-report symptoms simply as a result of study participation. At least one recent study of biases due to non-specific effects, such as the Hawthorne effect, on quality of life found that their influence is not clinically significant.[1]

In summary, the single-arm study design used was appropriate given FDA regulations for studies of medical devices, the nature of the intervention, the lack of study subjects' response to pharmacotherapy, and the lack of other standard procedures for AF. Several steps were taken to minimize potential contributions from sources of bias and artifacts.

2. "In Module 3 of the PMA submission, you provided a report of lesion comparison testing which was designed to demonstrate that the NavAblator™ creates lesions that were similar in depth and degree as legally marketed ablation catheters used in the clinical study. This bench testing did not include ample number of legally marketed (4 mm) radiofrequency ablation catheters. As previously outlined in an email sent on May 6, 2003, please provide the test results analysis from your catheter comparison teting with the appropriate sample size, which demonstrates the equivalence of the lesions created by the subject device and legally marketed catheters used in the clinical study."

A full lesion comparison study was performed, which showed that lesions created by NAVABLATOR® are of similar depth and width, after taking into account the catheter's slightly larger size, to other, commercially available catheters used for isthmus ablation. The study is briefly described below and included as Appendix A.

The initial report was too small to permit adequate comparisons. At the Agency's request, a larger study was performed using a protocol that was initially reviewed by the Agency, including the comparison devices. The study performed used a more standard statistical hypothesis (statistical equivalence) and the sample size was increased to 10 samples per catheter. Included are one catheter that is currently commercially approved for isthmus ablation (Webster Celsius), and a companion catheter (Blazer II) to one currently approved (Blazer XP). The study used a standard statistical approach to taking into account the slightly increased size of NAVABLATOR® (8 Fr) compared with five other catheters (7 Fr). The study results demonstrate substantial equivalence between lesions created by NAVABLATOR® and other tested hot-tip catheters.

3. "Please address the following with respect to the Customer Experience Reports described in P020039/A002, Volume 1, pages 37-38; Volume 2, pages 81-89, Table F43:

a. This table documents several electrical and cable failures, as well as coagulum formation. Please provide a detailed explanation of how you plan to address or

mitigate these failures in order to ensure appropriate catheter performance during actual use."

b. *This table documents several reports of the de-lamination of THV. The rational to address this issue is insufficient because you have not provided a reasonable explanation on [sic] how you plan to ensure the manufacturability and quality assurance of your catheters. Please provide a detailed explanation of how you plan to mitigate the de-lamination of THV in order to ensure the reproducibility and manufacturability of your catheters."*

Customer experience reports and resultant corrective actions are summarized below and described in detail in Appendix B of this letter. All investigations are complete. Manufacturing improvements in response to these reports, implemented between 1999 and 2001, were generally minor and involved steps to ensure the reproducibility and manufacturability of the catheters. Since these improvements, further failures have not been observed. A brief discussion is provided below with more details provided in the referenced Appendix.

During Phase IIB and III, 23 customer complaints were received concerning electrical and cable failures, coagulum and THV delamination. The previously submitted tables provided a preliminary description of our response to those complaints. To date, all customer complaints have been reviewed and all complaint investigations are currently closed. A summary of results of these investigations and corrective actions taken is provided below with further details provided in Appendix B. The complaints received were not of undue severity or frequency to merit concern. Manufacturing improvements aimed at addressing relevant changes were minor and ensure the reproducibility of manufacturing processes.

Electrical Failures

Sixteen failures occurred that were characterized as electrical in origin.

No corrective action was taken for the following reports:

- In five cases, failures were not reproducible
- In two cases, returned devices functioned normally; suspected failed cables were not available
- In one case, the cause could not be determined
- In two cases, devices were tampered with or cut, preventing determination of the failure cause
- In three cases, electrical noise was attributed to lack of appropriate electrical shielding in one clinical site's electrophysiologic equipment. The catheter probably served as a passive conductor of stray noise.

In two cases, the customer complaint was attributed to investigator mishandling. In one case (123), all wires connecting the catheter to the proximal connector were severed. In the other case (174), THV delamination occurred, probably as a result of overaggressive

16

cleaning. In both cases, instructions for use help the investigator to handle the devices properly. In addition, the THV process was improved (see below) to improve the robustness of the catheter to aggressive cleaning. No subsequent failures of this type have been observed.

Finally, one case (113) was attributed to manufacturing processes failure resulting in residual solder flux that was improved in 2002; a cleaning step was improved through the use of a magnetic strip that holds the catheter in place (see Appendix B for details). No subsequent failures of this type have been observed.

Cable Failures

Four cable failures were reported in three complaints.

In one, the cable functioned normally in our laboratory and the failure could not be reproduced.

In one case, the failure was attributed to the laboratory personnel not paying attention to the connector keyways that help with appropriate orientation of the connection. The role of these keyways was stressed to laboratory personnel and this failure has not recurred.

In one case, the cable failure was attributed to use of inappropriate techniques to remove the lead wire from the ECG monitoring system. Over two years ago the lead design was improved with a strain relief, improving robustness. This failure has not recurred.

Coagulum Reports

One investigator reported (91) mild coagulum formation after approximately 50 deliveries of RF energy. The IFU indicates not to deliver more than 50 RF applications with a single electrode. Coagulum formation occurs when tissue contact is suboptimal. Cardima sent a technical guidance document to study investigators, along with a published article reviewing a coagulum index.[2] No investigator has subsequently reported a similar problem. In two other cases (90 and 93), coagulum formation, probably as a result of THV delamination, prevented the physician from removing the catheter from its guide sheath. These cases were addressed via the THV manufacturing change (see below).

Delamination of THV

Four reports concerned THV delamination. On examination in our testing laboratory, all four cases showed roughness of the catheter and mild THV delamination. This was attributed to aggressive investigator cleaning of the catheter different from that recommended in the instructions for use. A minor manufacturing process improvement involving a heating/melting step was implemented in 1999, allowing the THV to flow into the coil interstices, resulting in a smooth THV transition over the coils. To date, no further complaints have been received regarding THV delamination.

In summary, investigations of customer complaints resulted in the following types of findings and actions:

17

Table 7. Summary of customer complaint finding and actions.

Finding	Action
Unconfirmed failures or device unavailable for testing	None
Electrical noise, probably resulting from the passive transmission through our catheters into equipment without appropriate filtering capability	None
Incorrect handling of devices	Lead design improved, technical guidance provided to investigators and laboratory personnel
THV delamination, single electrical failure due to residual solder flux	Minor manufacturing improvements

Since implementation of the minor manufacturing changes, no similar complaints have been reported. These minor changes, combined with multiple release-point checks during manufacturing, ensure the reproducibility and manufacturability of catheters.

4. "In Module 4 of the PMA submission, you provided incomplete documentation in order to support a 3 year shelf life for your devices. In the report, you indicate that aged samples failed tests and that tests should be repeated on samples having the corrective actions. However, no data were submitted on these samples. Please provide this documentation."

Failures observed in the previously reported shelf-life testing are reported below. None were age-related. All were determined to be related to manufacturing processes, which have been addressed. A repeat shelf-life validation study (see Appendix C) showed that these failures did not recur. The shelf-life testing performed is sufficient to ensure the requested three-year duration.

The section below describes in further detail failures previously reported in Module 4.

Among 34 catheters tested, in ten (see Section 5.5.2) the proximal connector end was observed to be extending by two to three centimeters out of the dispenser coil. In all cases the distal section of the catheter with the electrodes remained more than 145 cm deep in the protective spiral dispenser coil and showed no evidence of damage. Moreover, the protective primary sterile protection pouch was never compromised. All catheters were tested and were found to be functionally satisfactory. These observations suggest that the small extension was an aesthetic observation only, and was not expected to impact either device performance or sterility.

In 2002, a retainer clip was added to the dispenser coil as a corrective action, and this clip has been validated (ENG 02-1004-01). Product complaints relating to packaging of

REVELATION® Tx have not occurred, either before or after this change. Repeated shelf-life testing specifically aimed at this failure was deemed not necessary due to retainer clip validation and the fact that the failure was manufacturing-related, not age-related. In the subsequent three-year shelf-life validation report, these failures were not observed in 22 devices tested.

Among 34 catheters tested, 25 were observed with green discoloration at the solder junction (see Figure 1) connecting the internal catheter wires with the electrodes. All discolorations were observed to be underneath the covering THV laminate, meaning that blood contact would be extremely unlikely. Of the 25 catheters, two also showed electrode failures.

Both the discoloration and the electrical failures were attributed to insufficient removal of residual flux used for soldering, resulting from the catheter not remaining submerged for a sufficient period of time in cleaning fluid. The residual flux may have etched the conducting wire, causing the electrical failure. This failure, which is the same as that described above for customer report #113, was addressed in 2001 (CAR 2001-001), in which a magnetic strip was added to the manufacturing process, ensuring that the catheter remains submersed in cleaning fluid during the catheter cleaning step. Complete adherence to this process has been ensured through thorough re-training (MPI 00296) and further customer complaints attributable to this failure mode have not occurred. While the electrical failure occurred as a result of etching of residual flux into the copper conducting wires over time, the root cause of the failure was manufacturing-related and addressed with a manufacturing process improvement. All product built prior to the implementation of this corrective action has expired.

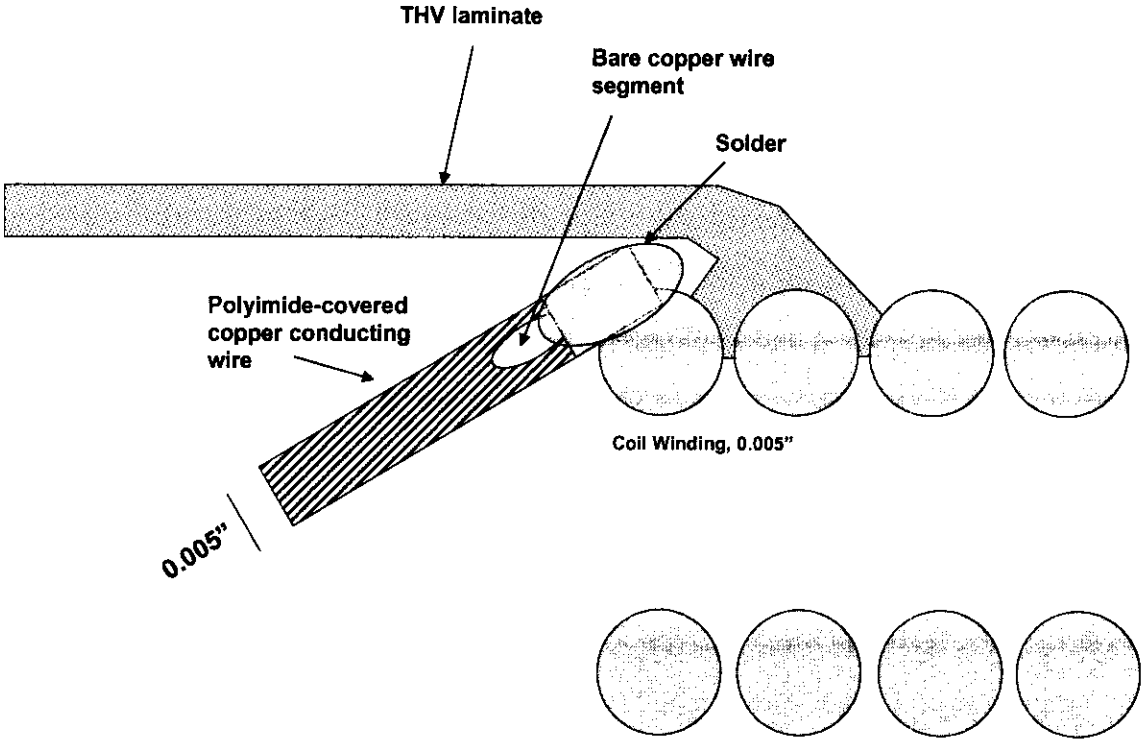


Figure 1. Schematic diagram showing catheter copper conducting wire connecting to catheter platinum electrode coil winding. Note that both copper conducting wire and platinum electrode coil winding are 0.005" in diameter and solder area is 0.003 – 0.005" in diameter.

Repeat Shelf-Life Validation

In December 1999, an addition 22 devices were set aside for real-time aging. Repeat shelf-life testing was performed per protocol ENP-02-1049 in January to March 2003, with additional testing through July 2003. Both the protocol and report (ENG-03-1049-02) are attached in Appendix C of the PMA amendment. This protocol differed from that previously reported to the Agency in the following aspects:

1. The new protocol added a conditioning requirement prior to aging, which exposes the product to more stringent conditions (temperatures of 5°C to 60°C and relative humidity of 50% - 90%) than simply aging.

2. VP-01879 required both accelerated aging and real time aging. The new protocol pertained to real time aging only.

3. VP-01879 included validation of the packaging. However, identical packaging has already been validated for a three (3) year shelf life according validation protocols ENG-01-1004 and ENG-01-1035-01. In retrospect, the packaging did not need to be revalidated as specified in VP-01879.

All aging tests were passed except for the following:

Five of 22 samples showed slight discoloration, determined to be copper oxide, on examination under a microscope. (Note this discoloration is different from the green discoloration observed in the prior shelf-life testing, which was due to residual flux.) All discolorations were again observed to be underneath the covering THV laminate, meaning that blood contact would be extremely unlikely. The catheter met the visual specifications outlined in the product specification for unaided eye and 10x microscopy inspection. Under a 40x microscope, uninsulated and/or exposed copper wire was observed at the solder joints. The area of oxidation was extremely small (0.003 – 0.005"). Root cause analysis determined that excess insulation was removed in preparation for electrode attachment, and the exposed copper wires were not sufficiently covered with solder after attachment to the electrodes, thus allowing the wires to discolor. The corrective action taken to address this problem (CAR 2001-001) included a revision to the manufacturing procedures to further specify covering uninsulated and exposed copper wire with solder. All manufacturing employees were retrained to MPI 01160, with specific attention placed on this instruction. No failures related to open circuits or discolorations have been reported since.

Biocompatibility testing was performed on the devices containing the discoloration. These tests (cytotoxicity, acute systemic toxicity, intracutaneous toxicity, and hemolysis) all showed acceptable results, according to ISO-10993 for an externally communicating device with limited blood contact. Initial biocompatibility testing for REVELATION® Tx included sensitization testing. Comparison of the four tests referred to above on aged samples with initial testing for REVELATION® Tx showed comparable results; all test results were acceptable. Therefore, repeating the sensitization test was deemed unnecessary.

One device had an open circuit at thermocouple 8. The device's remaining thermocouples and electrodes met specifications. Our root cause analysis determined that open circuit was a tolerance issue between the catheter strain relief outer diameter (OD) and the connector collet inner diameter (ID). The connector collet grips the catheter strain relief outer diameter (OD), creating a mechanical joint between the connector and the catheter shaft. This joint will assume the torsional or tensile load between the connector and the catheter shaft when the physician manipulates the catheter for placement. If the catheter strain relief OD is not large enough for the connect collet to grip, as was the case with the above device, the solder joints between the conducting wires and the connector pins will take all the load, and the conducting wires can become detached from the solder cups when tensile or torsional force is applied to the connector.

As with other failurea noted, the failure mode is manufacturing-related, not age-related. In a corrective action (CAR 2002-113) the catheter strain relief OD was increased from 0.115" to 0.170" so that the connector collet grips the catheter strain relief, preventing the severing of the conducting wires. This change was validated (ENG-01-1017-01) and a 100% in-process inspection of the catheter strain relief OD was implemented. Since this change, no complaints attributable to this failure mode have occurred.

In summary, results from two shelf-life validation protocols showed no failures with age-related root causes. A small number of manufacturing issues were addressed via minor

manufacturing process instruction changes. To date, no similar failures in the field have been reported. The two protocols provide ample evidence for a three-year shelf-life.

References

1. Bouchet, C., Guillemin, F. & Briancon, S. Nonspecific effects in longitudinal studies: impact on quality of life measures. *J Clin Epidemiol* **49**, 15-20 (1996).
2. Chan, E. K., Abati, A. L. & Vepa, K. Coagulum index predicts coagulum formation in right atrial radiofrequency energy delivery to ablate atrial fibrillation. *Pacing Clin Electrophysiol* **23**, 1856-8 (2000).

7 RESULTS

7.1 STUDY INVESTIGATORS

Sixteen sites participated in the Phase III investigations. Two sites recruited and screened subjects, but the subjects did not have sufficient episodes of symptomatic AF to qualify for ablation. Study sites and the number of subjects who underwent ablation at each site are listed in Table 13. The investigator participants were a mixture of actively practicing community electrophysiologists plus a few academic physicians. This wide spectrum of practitioners ensures the generalizability of the study's results.

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

Site ID	Principal Investigator	Clinical Investigational Site	Number of Procedures
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.

7.2 *SUBJECT CHARACTERISTICS*

7.2.1 Subject Accountability

Figure 6 provides the flow of subjects through the Phase III investigation. As of December 10, 2003, 178 subjects have been screened for trial participation. Sixty-one subjects failed screening, 46 due to insufficient symptomatic AF episode counts, twelve due to findings on transesophageal echocardiography (mostly left atrial size > five cm and rarely thrombus or patent foramen ovale) and three for other reasons. Sixteen subjects withdrew prior to ablation and three are currently undergoing the baseline monitoring period. Ninety-eight subjects have undergone ablation. Of these, five have been ablated in the last 4 months and their data have not been included in this analysis. In all, 93 subjects undergoing 95 procedures comprised the **procedure cohort**, i.e., the group of study subjects in whom procedure and safety analyses were performed.

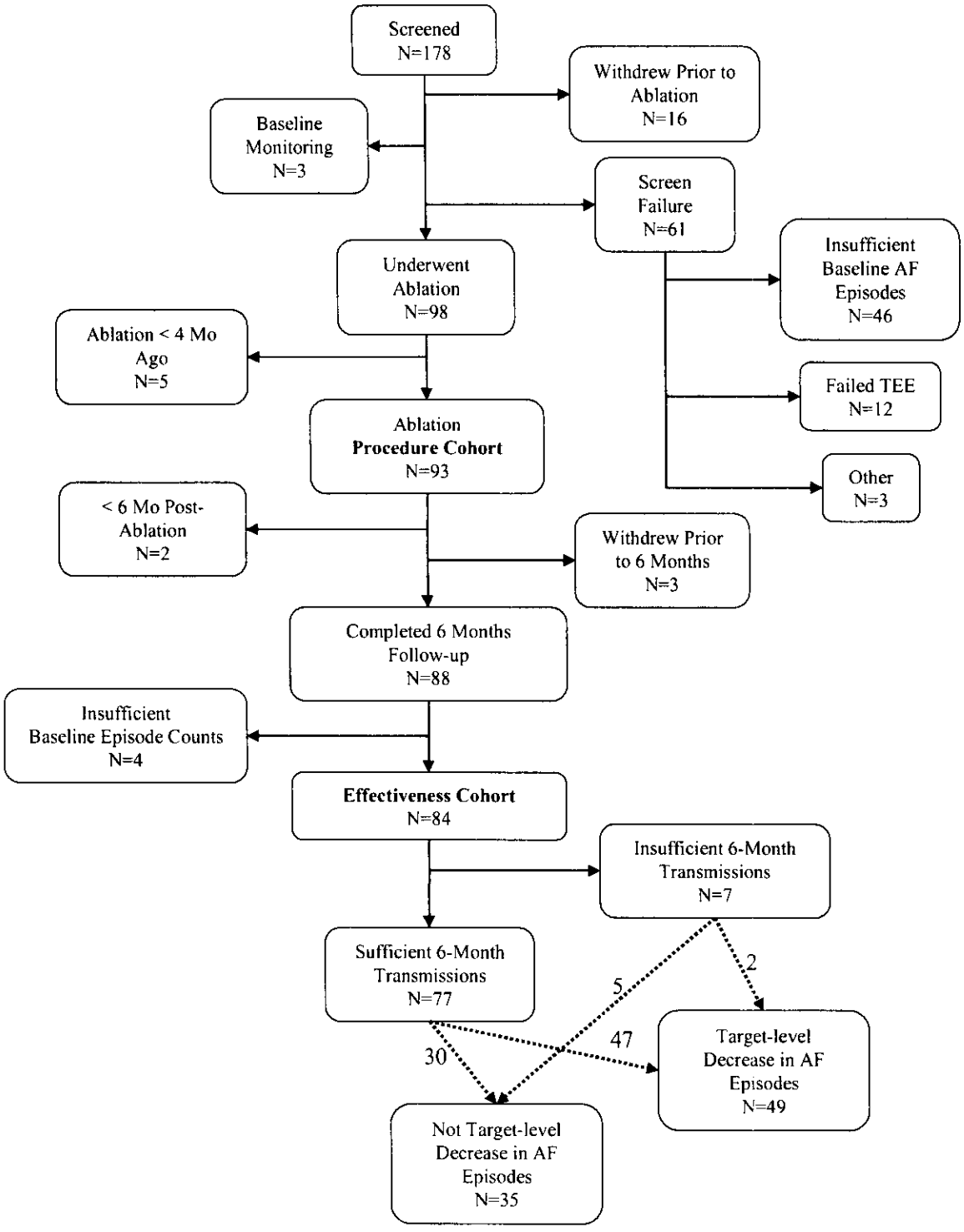


Figure 6. Subject accountability in Phase III study.

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

subjects are described in more detail below. Two subjects at one clinical site have been ablated in the past six months, and their six month outcome data are pending. Thus, eighty-eight subjects have completed six months of follow-up. Four of these subjects were omitted from episode analyses due to low baseline episode counts (described below), leaving 84 subjects who comprise the **effectiveness cohort**.

7.2.2 Study Withdrawals

As of December 10, 2003, seven subjects withdrew from the Phase III study prior to 24 months of follow-up. Of these, three withdrew prior to the six-month assessment (Table 14) and four withdrew after the six-month assessment (Table 15). The latter group contributed to the six month outcomes analyses presented below.

Table 14. Subjects who withdrew before 6 month study endpoint.

Subject ID	Comments	Days from Ablation to Withdrawal
	Subject's insurance did not cover treatment by study investigator. Voluntarily withdrew and underwent AV node ablation and PM placement at hospital covered under insurance	122
	Moved out of state	125
	Subject unwilling/unable to do follow-up, experienced anxiety/depression	157

Table 15. Subjects who withdrew after 6 month study endpoint.

Subject ID	Comments	Days from Ablation to Withdrawal
	Developed asymptomatic brady + 2-second pauses at 6 weeks. DDD placed two days after 6-month visit	132
	Pursued investigational drug treatment, DDDR at 8 months followed by AVN ablation at 10 months	312
	Developed atrial flutter then persistent AF, had AVN + VVIR at 3 months	286
	Moved to different country	110

All three subjects who withdrew prior to six months did so for non-study-related reasons. One moved out of state and one could no longer participate due to an

insurance change and non-coverage of the study site investigator. The covered provider recommended AV node ablation and pacemaker treatment for AF, which the subject received. One subject withdrew because anxiety and depression prevented full participation.

Of the four subjects who withdrew after the six-month endpoint, two were treated with AV node ablation and pacemakers and one withdrew for a non-study-related reason. The remaining subject (512) had asymptomatic pauses noted on study transmissions. Despite stopping beta-blockers, the subject continued to have sinus bradycardia and asymptomatic pauses. The subject underwent pacemaker placement two days after the six-month study visit for treatment of tachy-brady syndrome, which was noted by the investigator to be a pre-ablation condition, and not a result of catheter ablation.

7.2.3 Demographic Characteristics

In the procedure cohort, 93 subjects underwent RF ablation with the REVELATION® Tx. Mean subject age was 58 years (range 28 to 78) (Table 16). Seventy-four percent of subjects were male, and men were slightly younger.

Table 16. Descriptive statistics for age by gender

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

7.2.4 Medical Characteristics – Cardiovascular Disease

Sixty-nine (76%) subjects had some form of concomitant cardiovascular disease; however, due to exclusion criteria and screening, study subjects did not have significant structural heart disease. Table 17 provides details of prior cardiac interventions. Thirty subjects (32%) had previous RF ablation procedures; 24 were

for atrial flutter, 7 for AF and 4 for other indications.[f] On average, subjects reported a history of symptomatic AF for 5 years (range < 1 year to > 8 years, Table 18).

Table 17. Details of previous cardiac interventions (N=93).

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

*Some subjects had more than one prior cardiac intervention

Table 18. Duration of AF prior to ablation (N=93).

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

7.2.5 EKG Findings at Baseline

EKG findings were common at baseline, which was not unexpected given the study recruitment criteria (see Table 19). AF was present in 23 (25%) subjects and conduction abnormalities were common.

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

Table 19. EKG findings at baseline (N=93).

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

7.2.6 Medical Characteristics – Other Disease

Other concomitant disease was fairly common among study subjects (Table 20). Thirty-three percent had respiratory disease, 30% had endocrine disease and 45% had musculoskeletal disease.

Table 20. Frequency of concomitant baseline medical disease (N=93).

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

7.2.7 Baseline Cardiac Status

7.2.7.1 Functional Status

All subjects had good cardiovascular functional status, as indicated by New York Heart Association (NYHA) class ratings of I in 68 (74%) and II in 24 (26%) (Table 21).

Table 21. Baseline NYHA status (N=92).

NYHA Classification	Frequency	%
I	68	73.9
II	24	26.1

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

Despite good functional status, subjects reported frequent occurrence of symptoms related to AF at baseline (Table 22). Eighty-eight percent had palpitations, 58% fatigue, 49% shortness of breath, 36% lightheadedness and 21% chest pain.

Table 22. Baseline symptoms of AF episodes (N=93).

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

a) 1 response missing; b) 2 responses missing

7.2.7.2 Baseline Symptom Episode Frequency

Table 23 provides the distribution of baseline symptomatic episodes recorded using cardiac event monitors. Subjects with fewer than 3 episodes at baseline were not qualified to undergo RF ablation in this study. Twenty-seven subjects (29%) had 10 or more episodes at baseline; 11 (12%) had 20 or more at baseline. The mean (±SD) number of episodes at baseline was 9.7 ± 9.2.

Table 23. Distribution of number of symptomatic AF episodes occurring during the baseline 30-day monitoring period.

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

7.2.8 Baseline Quality of Life

Quality of life was assessed at baseline and follow-up periods using two instruments: the Medical Outcomes Study's Short-Form 36 (SF-36) and the Atrial Fibrillation Symptom Score.

7.2.8.1 SF-36 Scores

Table 24 provides a comparison of baseline SF-36 scores among subjects in the Phase III trial with those in a general US population. Compared to the general US population, REVELATION® Tx trial participants showed substantially lower role physical and vitality scores, consistent with the presence of symptomatic AF and a meaningful impact of AF on physical health.

Table 24. Comparison of SF-36 scores in Cardima clinical trials to other literature.

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

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

7.2.8.2 Atrial Fibrillation Severity Scale

Atrial Fibrillation Severity Scale (AFSS) scores were determined at baseline and in follow-up using an adapted version of Dorian's original instrument.[56] Table 25 provides descriptive statistics for scores for each question, adjusted to a 0-to-100 scale (higher scores indicates better health).

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

Table 25. Baseline AFSS scores by study phase.

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

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

7.2.9 Medications at Baseline

To qualify for ablation, subjects were required to have drug-refractory, symptomatic paroxysmal AF. Drug-refractory was defined as lack of clinical response, as judged by the investigator, to two or more AADs or to amiodarone alone. The requirement for drug refractoriness, which was consistent with the 1998 FDA Advisory panel recommendations for clinical trials of device-based treatment for AF, ensured that patients had exhausted all standard therapies before undergoing the investigational procedure. On average, subjects were refractory to 2.9 AADs (median 3). Medications to which subjects were refractory are shown in Table 26. Thirty-eight of 93 (41%) had tried and failed amiodarone.

Table 26. Generic drug names to which subjects were refractory at baseline.

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

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

7.3 PROCEDURE FEATURES AND RESULTS

Ninety-three subjects underwent 95 RF ablation procedures with the REVELATION® Tx Microcatheter system (two subjects underwent a second procedure, see below). The denominator for all procedure-related analyses is therefore 95. All procedures were performed between September 2000 and August 2003.

7.3.1 Sheath Insertion Site and Sedation Used

The RF ablation procedure was performed using standard venous access. In nearly all cases (92/95, 97%) access was via the right femoral vein. Conscious sedation was used in 57 of 95 (60%) procedures; subjects had general anesthesia in the remaining 38 (40%).

7.3.2 Rhythm at Procedure

At the start of the procedure, 25 (26%) were in AF, 55 (58%) were in NSR and 15 (16%) were noted to be in other cardiac rhythms (either sinus bradycardia or atrial flutter). During the procedure 42 (44%) underwent cardioversion with either medication treatment or DC energy.

7.3.3 Procedure Times

Mean (SD) procedure time was 218 (111) minutes; mean investigational catheter time was 162 (74) minutes; mean fluoroscopy time was 43 (42) minutes (see Table 27, Table 28, Table 29, respectively). There was modest variation of procedure, investigational and fluoroscopy time across study sites. However, such variation was expected due to use/non-use of different mapping techniques, and the use of different baseline electrophysiologic testing procedures, both of which were allowed by the study Protocol. Across sites, maximum procedure times ranged from 131 to 549 minutes.

Table 27. REVELATION® Tx procedure time by study investigator (N=95).

	Frequency	Procedure Time				
		Mean	Std	Min	Median	Max
Investigator						
3	2	270	7	265	270	275
5	8	163	46	104	167	229
6	4	348	98	250	332	478
8	1	131	-	131	131	131
10	8	185	50	107	180	241
11	4	314	102	225	284	461
14	19	131	26	100	125	190
15	1	209	-	209	209	209
16	15	221	75	130	203	421
17	4	372	120	285	326	549
18	5	406	140	247	494	530
19	4	157	7	150	156	165
21	5	265	49	192	272	330
23	15	193	44	112	200	268
Total	95	216	100	100	190	549

Table 28. REVELATION® Tx investigational catheter time by study investigator (N=95).

	Frequency	Investigational Catheter Time				
		Mean	Std	Min	Median	Max
Investigator						
3	2	180	21	165	180	195
5	8	107	29	70	105	168
6	4	263	78	160	282	330
8	1	113	-	113	113	113
10	8	172	54	81	166	235
11	4	206	56	155	194	280
14	19	124	24	99	120	180
15	1	189	-	189	189	189
16	15	187	79	95	170	406
17	4	291	136	165	262	475
18	5	201	111	111	155	385
19	4	128	17	112	125	152
21	5	164	63	108	154	260
23	15	130	53	35	126	233
Total	95	162	74	35	143	475

Table 29. REVELATION® Tx fluoroscopy time by study investigator (N=95).

	Frequency	Fluoroscopy Time				
		Mean	Std	Min	Median	Max
Investigator						
3	2	61	8	55	61	66
5	8	26	5	20	24	34
6	4	16	7	10	15	26
8	1	20	-	20	20	20
10	8	18	4	14	17	27
11	4	42	3	39	43	45
14	19	20	7	11	18	42
15	1	38	-	38	38	38
16	15	39	19	15	37	95
17	4	109	65	64	84	204
18	5	154	85	73	131	265
19	4	74	22	52	70	102
21	5	81	15	55	90	90
23	15	27	11	13	26	54
Total	95	43	42	10	28	265

7.3.4 Study Catheters

7.3.4.1 Linear Lesions

In all study procedures, REVELATION® Tx alone was used to create linear lesions in the right atrium.

7.3.4.2 Isthmus Ablation Catheters

The protocol required ablation of the tricuspid-cavo isthmus in order to prevent atrial flutter in follow-up and to treat a potential substrate or site of origin for AF. In Phase III, NAVABLATOR®, a hot-tip catheter that produces lesions similar to other hot-tip catheters,[h] was added as the recommended ablation catheter for the isthmus line. If the Cardima catheter could not be used successfully to ablate the isthmus, the Protocol permitted the use of standard institutional procedures to complete the

[h] See attached in vitro comparison of NAVABLATOR® and other hot-tip catheters.

isthmus line. (Note that in January 2003, Cardima notified investigators that NAVABLATOR® should be the sole catheter used in the procedure).

In Phase III, NAVABLATOR® was used in 77 of 89 (87%) procedures in which isthmus ablation was attempted (see Table 30). (Note that 6 subjects in Phase III had previous isthmus ablations; the Protocol did not require isthmus retreatment.) NAVABLATOR® was the first catheter used in 71/89 (80%) of procedures. In 14 procedures (16%) REVELATION® Tx was used as the initial catheter, which was permitted by the study Protocol. In four procedures (3 at one site, 1 at another), a study catheter was not used initially to ablate the isthmus (Table 31). In the remaining 85 procedures (95%), study-related catheters were used initially.

Table 30. Isthmus catheters used in Phase III.

Isthmus Catheter Used	Frequency	%
NAVABLATOR®	51	57.3
NAVABLATOR®, then Other	20	22.5
REVELATION® Tx	8	9.0
REVELATION® Tx, then NAVABLATOR®	3	3.4
REVELATION® Tx, then NAVABLATOR®, then Other	3	3.4
Other	4	4.5
Total	89	100.0

Table 31. Non-investigational study catheters used initially to ablate the isthmus.

Catheter name	Frequency
Navistar (Biosense)	1
Atakr (Medtronic)	1
Marinr (Medtronic)	2

In 23 cases, bidirectional conduction block was not achieved with study-related catheters alone (NAVABLATOR® or REVELATION® Tx) (Table 30). Table 32 shows a list of other catheters used to ablate the isthmus when it could not be achieved with study catheters alone.

Table 32. Other catheters used to complete isthmus ablation when NAVABLATOR® or REVELATION® Tx were not used.

Catheter Used	Frequency
Blazer II (Boston Scientific)[a]	10
Navistar (Cordis)[b]	5
MARINR (Medtronic)	5
Cooltip (Cardiac Pathways)	1
Stinger (Bard)	3
Total	23

a) Blazer II is legally marketed for the interruption of accessory atrioventricular conduction pathways associated with tachycardia, AV nodal reentrant tachycardia, and for AV nodal ablation in AF with rapid ventricular response; Blazer II XP, an 8 mm variant of Blazer II, is legally marketed for isthmus ablation for atrial flutter

b) Legally marketed for the creation of isthmus lesions in atrial flutter. Two other catheters used in one case.

7.3.5 Procedure Endpoints

7.3.5.1 Amplitude Reductions

In a July 1998 Advisory Panel meeting on the design of clinical trials of AF, it was noted that no acute physiologic endpoint existed for AF procedures that denoted the achievement of a specific outcome indicating that the procedure was complete. Acknowledging this, the study Protocol required investigators to document a proxy measure: reduction of the amplitude of atrial electrogram amplitudes after ablation. The protocol required documentation of paired before- and after-ablation measurements for each electrode for each lesion created.

Amplitude reductions were measured in 83 of 95 (87%) procedures performed in Phase III. On occasion before-after measurements were not paired by electrodes; in all, 74 of 95 (78%) procedures had electrode-paired measurements. Table 33 shows mean atrial electrogram amplitudes before and after the procedure. On occasion, the REVELATION® Tx catheter is placed with its distal or proximal electrodes outside of the electrically active portion of the right atrium; in this case, ablation is carried out on fewer than eight electrodes. This explains why there are fewer subjects in whom electrode measurements were performed than lesion measurements.

Table 33. Paired atrial amplitude measurements before and after ablation procedure.

	Number of Subjects	Number of Measurements	Electrogram Amplitude, Before (mV)			Electrogram Amplitude, After (mV)		
			Mean	Std	Median	Mean	Std	Median
Lesion								
Posterolateral	74	504	1.31	1.98	0.68	0.77	1.87	0.40
Septal	68	424	1.62	3.09	0.92	0.96	2.85	0.50
RF Electrodes								
1	41	105	1.28	2.04	0.62	0.88	2.21	0.40
2	56	128	1.00	1.16	0.64	0.55	0.58	0.39
3	43	110	1.72	2.88	0.93	1.22	3.18	0.47
4	58	134	1.34	1.33	0.93	0.65	0.77	0.44
5	44	109	2.16	4.35	1.10	1.61	5.31	0.50
6	58	133	1.44	1.42	1.00	0.60	0.56	0.41
7	40	101	1.60	4.11	0.60	0.86	1.56	0.40
8	54	108	1.21	1.32	0.61	0.65	0.70	0.40

The table shows measurements of amplitudes for posterolateral and septal lesions created by REVELATION® Tx only. Since the REVELATION® Tx catheter is occasionally placed with its distal or proximal electrodes outside of the electrically active portion of the right atrium, the number of subjects with particular electrode measurements may be smaller than the number of subjects with lesion measurements.

Figure 7 shows a plot of atrial electrogram amplitudes after the procedure vs. before the procedure. The majority of the points are below the identity line, indicating that ablation has reduced the measured amplitudes in most cases. The "scatter" of the plot indicates that amplitude reduction is subject to substantial variation across subjects (see below for discussion).

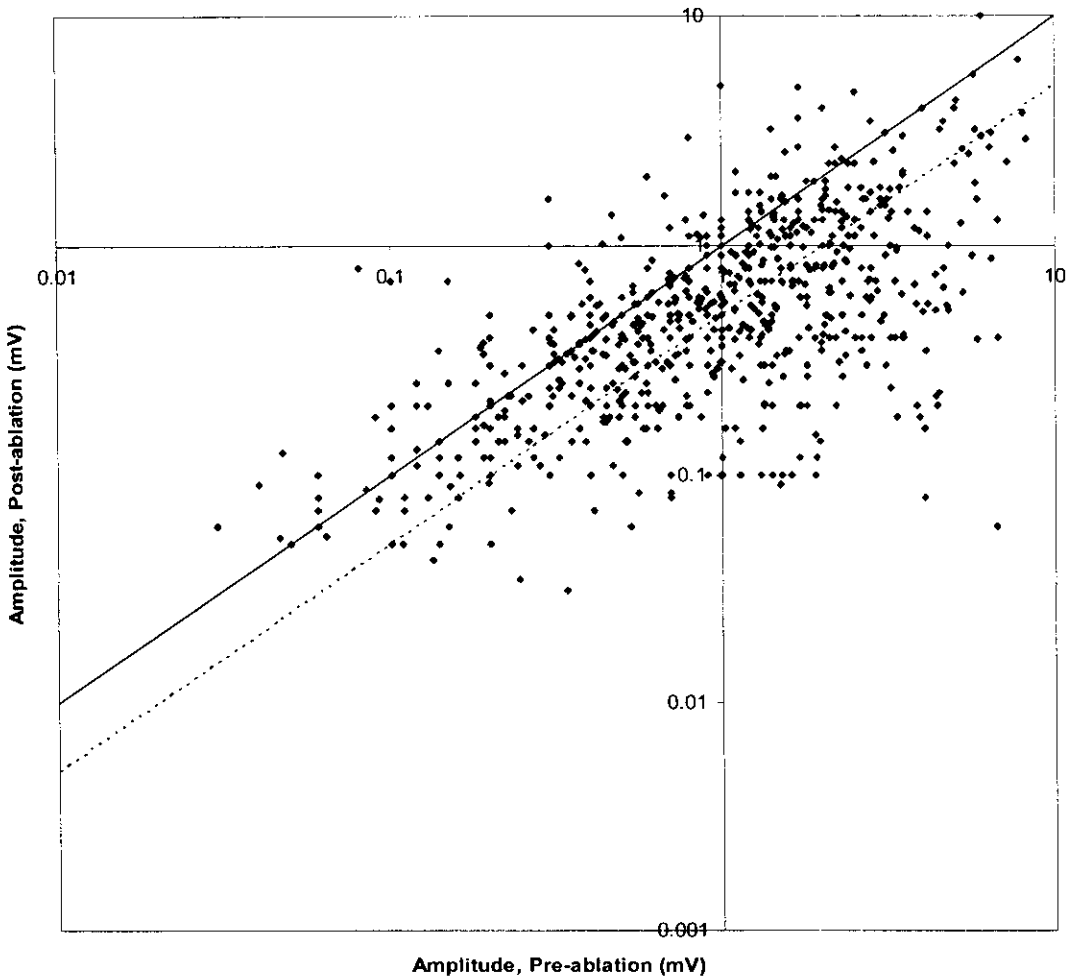


Figure 7. Plot of post-ablation amplitude vs. pre-ablation amplitudes in Phase III subjects with paired pre-post measurements.

Values under the dark identity line show electrode measurements in which the post-procedure value is lower than the pre-procedure value. Values under the dotted line show measurements whose post-procedure value is less than half of the pre-procedure value.

Using a hierarchical mixed model regression approach, mean reduction in log amplitude (mV) was 0.36, indicating that, on average, measurements made after the ablation were 44% (i.e., $10^{-0.36}$) as large as those prior to ablation, demonstrating that ablations using REVELATION® Tx resulted in a substantial (56%) decrease in atrial electrogram amplitudes. Regression models included a random term for study investigator (since there was variation in both mean reduction and pre-ablation

amplitude across investigators). In addition, all regressions were performed on the log scale since data were log-normally distributed.

Discussion. While pre- and post-procedure amplitude measurements are of interest, several caveats should be applied to these data.

Inexact measurements. Before-after measurements of atrial amplitudes may be inaccurate and are likely to underestimate the true amount of amplitude reduction caused by ablation. Before-ablation measurements took place before any application of RF energy, and after-ablation measurements were generally recorded after RF energy had been applied through all targeted electrodes for the particular lesion. If the subject coughs, talks or otherwise moves during ablation, the catheter location may change; this would result in the post-ablation measurement being artificially high, since tissue located more than a few millimeters from the point of electrode contact remains intact. With ablation, the mass of atrial tissue in contact with the electrode may change. In addition, endocardial conduction velocity near the electrode and the vector of conduction direction can also change after ablation. All of these changes can potentially affect the post-ablation measurement, most likely inflating its value. Consequently, the post-ablation measurement is likely to represent both a "rough approximation" and a minimum change.

Not necessarily relevant measurement. In its typical application, endocardial ablation targets a single myocardial focus of reentry using a single electrode at the catheter's tip. The ablation target is a single focus of reentry. When successfully ablated in these procedures, the electrogram is visibly different than that recorded by adjacent electrodes, usually showing an absence of electrical activity at the ablation location.

The goal of linear ablation for AF is substantially different. Rather than a single focus, the target of ablation is substrate modification and the creation of lines of block using a multi-electrode catheter. At the time of trial design (and arguably even today), there was no accepted measurement for determining whether a line of block has occurred. Measurement of a decrease in atrial electrogram amplitudes along the

lesion location clearly demonstrates that atrial endocardial tissue has been ablated. However, while the design of the REVELATION® Tx catheter promotes the creation of lines of block in the atrium, measurement of atrial electrogram amplitude reductions does not guarantee that a line of block has been successfully created. While newly developed contact- and non-contact mapping techniques can show these lines of block, these expensive technologies are not standard of care; moreover, whether using these techniques to demonstrate such lines is predictive of long-term patient success has not been shown. Theoretically, the ablating catheter may be placed orthogonally to the ablation line just created; pacing can be done on one side and measurement on the other. However, the flow of electrical signals crossways to the lesion is difficult to predict; whether the change in electrical flow from before to after the line creation is predictive of long-term success is not known. Due to the lack of a convenient and clinically relevant endpoint, a decrease in atrial electrogram amplitudes was selected as a proxy measurement. It is possible that the perceived lack of predictive value of these lines explains why not all investigators consistently recorded these data.

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

7.3.5.2 Bidirectional Conduction Block and Long-Term Success

The acute procedural endpoint of isthmus ablation was bidirectional conduction block (BDC). BDC indicates that the flow of electrical impulses through the isthmus on pacing in the coronary sinus has been blocked. BDC may be an important outcome in the treatment of atrial flutter. However, whether the achievement of BDC in isthmus ablation helps to prevent recurrent AF episodes is not known.

In all, BDC was demonstrated in 74 of 89 (83%) subjects in whom isthmus ablation was attempted. (Six subjects had prior isthmus ablation, and the Protocol did not require repeat isthmus ablation.) Among subjects in whom isthmus block was attempted initially with NAVABLATOR®, BDC was established in 45 of 71[i] (63%) using NAVABLATOR® alone. When another catheter was also used, BDC was demonstrated in 60 of 71 (85%). Similarly, among subjects in whom REVELATION® Tx was used initially, BDC was demonstrated in 7 of 14 (50%) using study catheters (REVELATION® Tx or NAVABLATOR®) only. In 3 cases, use of another catheter was required to achieve BDC.

Table 34. Number of subjects in whom bidirectional conduction block was demonstrated or attempted by isthmus catheter used.

	Bidirectional Conduction Block	
	Demonstrated	**Attempted**
NAVABLATOR®	45	51
NAVABLATOR® then Other	15	20
REVELATION® Tx	4	8
REVELATION® Tx then NAVABLATOR®	3	3
REVELATION® Tx, NAVABLATOR®, then Other	3	3
Other	4	4
Total	74	89

The relevance of BDC to long-term treatment success in catheter ablation of AF is not known. As discussed further in a section below, the reduction in symptomatic AF episodes was higher among subjects in whom BDC could <u>not</u> be demonstrated (88% vs. 51%, $p < 0.001$, Fisher's exact test, see Table 35). (For complete reporting of successful reduction of AF episodes, see the section entitled "Episode Reduction" below.) This finding highlights the fact that the physiologic measurement used to judge success of isthmus ablation may not be particularly relevant to procedures aimed at the treatment of AF. Similarly, subjects in whom a non-study catheter was

[i] 51 (NAVABLATOR®) + 20 (NAVABLATOR® plus other)

used were not more or less likely to show successful reduction in symptomatic episodes at 6 months.

Table 35. Episode reduction success rates by achievement of bidirectional conduction block.

Bidirectional conduction block achieved	Demonstrated/Attempted*	% Success
No	14/16	87.5
Yes	33/65	50.8
Total	47/81	58.0
Isthmus catheter used		
NAVABLATOR®	24/45	53.3
NAVABLATOR® then Other	11/18	61.1
REVELATION® Tx	7/8	87.5
REVELATION® Tx then NAVABLATOR®	1/2	50.0
REVELATION Tx, NAVABLATOR®, then Other	1/2	50.0
Other	1/4	25.0
Total	45/79	57.0

*Excludes subjects in whom isthmus ablation was not attempted since it had been performed prior to study entry.

Bidirectional conduction block (BDC) was the primary physiologic endpoint used to determine whether an isthmus ablation was a success. BDC was achieved with study catheters alone less often than expected, requiring investigators to use non-study-related catheters to complete BDC. The lower success rate was attributed primarily to non-use of a flutter sheath. Flutter sheaths are guiding catheters used specifically to position ablation catheters. Use of a flutter sheath with NAVABLATOR® extends its reach, allowing the investigator to place the tip of NAVABLATOR® into the right ventricle, as required by the Protocol. As the trial progressed, it was observed that investigators did not make sufficient use of flutter sheaths, and such use was promoted via newsletters mailed to study sites. The observed rate of achieving BDC with NAVABLATOR® alone (63%) was probably consistent with the expected rate, given non-use of flutter sheaths. The rate would likely have been higher had flutter sheaths been used consistently.

Notably, isthmus ablation is performed to prevent atrial flutter, not AF. Subjects who had successful ablation were not more likely to be treatment successes (i.e., achieve target-level reductions in the six-month symptomatic AF episode counts). Therefore,

the relevance of the decreased BDC rate with study catheters observed in this study to actual patient outcomes is quite low. This should be kept in mind when evaluating the overall performance of the REVELATION® Tx system.

7.3.5.3 Conductivity

Investigators measured A-H and H-V intervals before and after the procedure, in order to determine whether there was any damage to critical conduction pathways. Ranges and mean values for A-H and H-V intervals did not appear to change after ablation, indicating no apparent clinical effect on standard conduction pathways (Table 36).

Table 36. A-H and H-V intervals before and after ablation.

Electrographic feature	N	Mean	StdErr	Min	Max
Pre Ablation, A-H Interval (msec)	83	100.2	3.9	39	266
Post Ablation, A-H Interval (msec)	84	96.6	3.1	34	196
Pre Ablation, H-V Interval (msec)	86	53.1	1.8	24	129
Post Ablation, H-V Interval (msec)	86	52.8	1.4	24	105

7.3.6 Lesion Sets

The Phase III protocol defined a standard lesion set, referred to as ABC, that included[j]:

A. Inferior vena cava (IVC) to superior vena cava (SVC) posterolaterally
B. SVC to IVC posteroseptally
C. Isthmus line, IVC to tricuspid annulus (TA)

Previously a variety of lesions sets were reported. In July 2003 study site coordinators and investigators were asked, through routine data query practices established at the initiation of the clinical study, to review operative notes and case report forms (CRFs). In several cases, investigators appeared to have misunderstood the CRFs, marking categories that did not conform to the procedures actually

[j] Due to fear of AV node damage, the Phase III study eliminated the anterior "D" lesion (September 22, 2000).

111

performed. Investigators' written responses helped to clarify lesion sets actually performed in Phase III subjects. When reanalyzed, it was found that no investigator created what could be considered an anterior ("D") lesion, and lesions created (Table 37) conformed to the target set in all cases. Note that six subjects had prior isthmus ablation ("C") and did not undergo repeat ablation; also, one subject had a second procedure in which the isthmus only was ablated.

Table 37. Lesion sets performed.

	Frequency	%
Composite lesion lines ablated		
AB	6	6.3
ABC	88*	92.6
C	1*	1.1
Total	95	100.0

A = lateral; B = septal; C = isthmus
*one repeat procedure each

7.3.6.1 Second Procedures

Only two subjects at one site underwent repeat ablation procedures in Phase III; both repeat procedures were for atrial flutter. One subject ( ) had a repeat isthmus ablation at 175 days after the initial procedure. This was done for recurrent atrial flutter. The other subject underwent repeat ablation at 223 days after the initial procedure. The subject had experienced atrial flutter (symptoms unknown). In the electrophysiology laboratory, the subject was found to have atypical atrial flutter and she went into AF during the procedure. "Gaps" were noted using non-contact mapping techniques in the isthmus line as well as the lateral and septal lines; these were "touched up" using NAVABLATOR®. The final procedural diagnosis was atrial flutter. The six-month episode counts used for this were based on a monitoring period six months after the second procedure. Note that in many published study reports, a large proportion of subjects undergo more than one ablation procedure. In contrast, in the current investigation, only two subjects underwent repeat procedures.

7.3.7 Catheter Performance

Investigators evaluated REVELATION® Tx catheter performance on five fundamental characteristics (see Table 38). Overall catheter performance was rated very good to excellent 82% of the time. All five of the fundamental characteristics were rated good to excellent in more than three-quarters of the ratings.

Table 38. Investigators' performance evaluation of REVELATION® Tx Microcatheter.

		Rating (%)				
	N	Excellent	Very Good	Average	Fair	Poor
Performance Characteristic						
Ease of Placement	93	38.7	36.6	22.6	2.2	-
Stability of Placement	93	46.2	32.3	17.2	4.3	-
Radiopacity	93	51.6	30.1	14.0	4.3	-
Pacing[a]	79	30.4	34.2	32.9	-	2.5
RF Energy Application	93	41.9	46.2	9.7	2.2	-
Overall Performance	93	40.9	41.9	14.0	3.2	-

a) Pacing not evaluated by all investigators

Pacing received the weakest evaluation, with only 51 of 79 (65%) respondents rating it good to excellent. It was thought that investigators were unaccustomed to pacing with the 3.7 Fr REVELATION® Tx as opposed to the conventional 7 Fr ablation catheter. Pacing with the REVELATION® Tx requires less mechanical force to achieve appropriate contact with the endocardial tissue than the conventional catheter, so there is a different feel initially. The REVELATION® Tx catheter is also configured differently for pacing than the conventional ablation catheter, having eight electrodes rather than the two at the tip, proximal and distal, normally used for bipolar pacing.

Table 39 shows evaluation results for the NAVABLATOR®. Overall performance of the NAVABLATOR® was very good to excellent in 42% and average to excellent in 63%. Ease of placement and ease of deflection were rated very good to excellent in 44 and 48%, respectively. All other ratings were very good to excellent in 50% or more, and average to excellent in 80% or more.

The relatively lower ratings for NAVABLATOR® were attributed to a sub-optimal deflection mechanism, which has been improved during the course of the investigation, and non-use of flutter sheaths. The Protocol-allowed standard institutional procedure using conventional 7 Fr tip ablation catheters included use of a guiding sheath to enhance stability and access or reach. Investigators who used the NAVABLATOR® did not realize initially that they could use such a sheath with the investigational device as well, which would have enhanced the performance of the NAVABLATOR® in the same way a guiding sheath enhances the performance of a conventional catheter. When a guiding sheath was used with the NAVABLATOR®, bi-directional block can be more readily achieved.

Table 39. Investigators' performance evaluation of NAVABLATOR®.

		Rating (%)				
	N	Excellent	Very Good	Average	Fair	Poor
Performance Characteristic						
Ease of Placement	81	23.5	21	22.2	18.5	14.8
Ease of Deflection	81	28.4	19.8	13.6	22.2	16
Stability of Placement	81	27.2	23.5	30.9	9.9	8.6
Stability of Deflectable Tip	80	26.3	26.3	30	6.3	11.3
Radiopacity	80	50	28.8	20	1.3	-
Pacing[a]	57	35.1	28.1	36.8	-	-
Energy Application	77	35.1	23.4	27.3	9.1	5.2
Overall Performance	79	27.8	13.9	21.5	25.3	11.4

a) Pacing not evaluated by all investigators

Discussion. Performance of linear catheter ablation with REVELATION® Tx Microcatheter system was accomplished via standard electrophysiologic techniques for sedation and cannulation, and used a standardized target lesion set. Procedure time was fairly long in the Phase III clinical trial; however, much of the added length was due to the extra burden of measurement associated with the clinical trial and would not be expected in clinical practice. With development of a more sophisticated switchbox (in progress at Cardima), the entire procedure is estimated to take one to two hours.

During the clinical trial, use of non-study-related catheters was kept to a minimum. REVELATION® Tx, the primary technology tested in the trial, was used in 100% of linear lesions created. Lesion sets created were uniform across study subjects. The primary procedure-related outcome for the creation of linear lesions with REVELATION® Tx, the measurement of decreases in atrial electrogram amplitudes, was documented in most subjects; the mean decrease of 56% suggested that the study procedures accomplished the targeted ablation in the majority of cases. Whether complete lines of block were created was not determined in the clinical trial; whether contact- or non-contact mapping techniques can show lines of block, and whether such demonstration predicts long-term patient success, is not known. There was no evidence that initial or eventual use of non-study-related catheters was associated with overall worse patient outcomes. The primary indicator of success for isthmus line ablation did not appear to correlate with long-term patient outcomes. The lack of apparent relevance of BDC and other isthmus catheters in long-term outcomes should play a role in the consideration of the use of non-study-related catheters. Catheter performance was rated good to excellent in most cases for both REVELATION® Tx and NAVABLATOR®.

7.4 EPISODE REDUCTION

7.4.1 Effectiveness Cohort

Ninety-three subjects underwent linear RF ablations with the REVELATION® Tx Microcatheter system in Phase III. As depicted in Figure 6, 88 have completed six months of follow-up. Six-month study visits for two subjects ablated in summer 2003 have not yet occurred and have not been included in this study report.

As reviewed in the Protocol description, in order to standardize the reading of rhythm strips across the study, the monitoring service's cardiologist independently assessed all rhythm strips recorded by subjects; his determination of the cardiac rhythm underlying all episodes was used for all effectiveness analyses. Note that the cardiologist's interpretations were not generally available to study site investigators and were not used by study investigators at the baseline visit to determine whether a subject qualified for ablation. In four subjects, the monitoring service cardiologist

interpreted the set of baseline rhythm strips as having an insufficient number of symptomatic AF episodes (Table 40). In three of these cases, the study site noted the occurrence of four to nine episodes during the 30-day baseline monitoring period; however, when interpreted by the monitoring service's consulting cardiologist, the number of symptomatic episodes that showed AF was determined to be less than three, the qualifying threshold. Similarly, in one subject [redacted], baseline AF episodes measured during a 30-day monitoring period did not meet the required three episode threshold; during extended baseline monitoring, nine episodes that represented AF were noted by the site investigator. However, upon review by the monitoring service's cardiologist, only eight episodes were considered to be AF, which did not meet the study entry episode threshold. After excluding these four subjects, there were 84 subjects with evaluable six month data who comprised the **effectiveness cohort** in whom success rate calculations were performed.

Table 40. Number of symptomatic AF episodes for subjects whose episode data were excluded.

Subject ID	Site's Baseline Records	Monitoring Service Baseline Records
[redacted]	4	2
	6	2
	9	2
	9	8

7.4.2 Study Subject Compliance

Compliance with event monitoring was promoted by requiring that subjects record and transmit rhythm strips at least once per week, independent of the occurrence of symptoms. Since the event monitor can record more than one strip and some subjects with few episodes may have stored several strips in the event monitor without transmitting, it is also important to additionally examine the number of recorded strips during event-monitoring periods.

During the three- and six-month monitoring periods, respectively, 71 (85%) and 69 (82%) of 84 subjects in the effectiveness cohort transmitted rhythm strips at least three times and 62 (74%) and 60 (71%) subjects transmitted rhythm strips at least

four times. During the three-month monitoring period, only 2 subjects (2.4%) did not transmit any compulsory weekly strips or strips associated with symptomatic episodes. During the six-month monitoring period, only 7 of 84 (8%) subjects did not transmit any compulsory weekly strips or episode-related strips (see Table 41). From the perspective of six-month episode counts, these seven subjects can be considered non-compliant.

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

Table 42 provides the number of rhythm strips (as opposed to transmissions) recorded and transmitted in the Phase III study. During the three- and six-month monitoring periods, respectively, 83% and 77% of subjects recorded four or more strips and 93% and 88% recorded three or more strips.

Table 42. Number of strips recorded and transmitted to the monitoring service during the three and six-month monitoring periods (N=84).

Number of Strips	Month 3		Month 6	
	Frequency	%	Frequency	%
0	2	2.4	7	8.3
1	4	4.8	0	0
2	0	0	3	3.6
3	8	9.5	9	10.7
4 or more	70	83.3	65	77.4
Total	84	100.0	84	100.0

Table 43 shows a comparison of number of rhythm strips recorded by subjects in months three and six of follow-up in Phase IIB vs. Phase III. Compliance improved substantially in Phase III compared to Phase IIB.

Table 43. Comparison of rhythm strip monitoring during months 3 and 6 in Phase IIB vs. Phase III.

Number of Strips	Study Phase			
	IIB		III	
	Frequency	%	Frequency	%
Month 3				
0	2	6.5	2	2.4
1	2	6.5	4	4.8
2	6	19.4	0	0.0
3	4	12.9	8	9.5
4 or more	17	54.8	70	83.3
Total	31	100.0	84	100.0
Month 6				
0	8	25.8	7	8.3
1	2	6.5	0	0.0
2	2	6.5	3	3.6
3	6	19.4	9	10.7
4 or more	13	41.9	65	77.4
Total	31	100.0	84	100.0

A summary of the clinical experience of the seven subjects who were non-compliant with six-month monitoring is provided in Table 44. Of these, two

reported improvements in AF frequency by two or more categories in the AFSS frequency subscale and were considered successes despite not participating in rhythm strip monitoring during the sixth month after ablation.

Table 44. Summary of outcomes among subjects who transmitted no rhythm strip data in the sixth month.

	Baseline Episode Information		AFSS Frequency Subscale Responses			
Subject ID	**Total strips**	**Sympto-matic AF Episodes**	**Baseline**	**Six Month**	**Comments**	**Final Determination (S/F)***
	7	4	(3) Daily or almost daily	(2) More than twice per day	AVN ablation + DDD pacemaker at 128 days for progressive AF	F
	4	4	(7) About twice a month	(7) About twice a month	3-month office notes showed "no symptomatic sustained AF", "very infrequent palpitations, last a very short time, not enough to make a recorder [sic]". 12-month CRF showed 40 episodes in last 6 months	F
	13	9	(3) Daily or almost daily	(6) About once a week	6-month visit office notes showed two AF episodes reported with mild palpitations. 12-month visit CRF showed 15 episodes in last 6 mo	S
	15	9	(2) More than twice per day	N/A	6-month office notes showed four AF episodes with palpitations, shortness of breath and fatigue. AVN ablation + PM at another clinical site at 8 months due to chronic AF	F
	6	6	(5) 2 to 3 times per week	(5) 2 to 3 times per week	Developed atrial flutter then persistent AF, had AVN + VVIR at 3 months	F
	10	3	(5) 2 to 3 times per week	(5) 2 to 3 times per week	Office notes showed attempts to improve compliance. 12-mo CRF showed 72 episodes in last 6 months	F
	16	9	(2) More than twice per day	(8) About once a month	Femoral AV fistula repaired, event monitor lost but not reported to study site. 6-month office visit notes no palpitations or arrhythmia symptoms during the last four months	S

* S = Success; F = Failure

7.4.3 Episode Detection

In patients with paroxysmal AF who experience symptomatic episodes, the underlying rhythm is not necessarily AF; it could be atrial flutter or other atrial or ventricular arrhythmias, or even normal sinus rhythm. In the case of NSR, the episode would be attributable to other medical problems, not arrhythmia. Table 45 provides the mean and median percentage of recorded episodes occurring during the baseline, three- and six-month monitoring periods that turned out, after review by the monitoring service's independent cardiologist, to be AF. At baseline as well as follow-up, the majority of episodes experienced were associated with AF. Note that subjects reported that, in follow-up, some episodes were brief; by the time the episode could be recorded, sinus rhythm may have returned. Taken as a whole, these results suggest that subjects were good at both detecting and recording episodes of AF and distinguishing them from other arrhythmias or underlying causes.

Table 45. Mean and median percentage of symptomatic episodes that were AF.

Monitoring Period	N*	Mean (%)	Median (%)
Baseline	84	79	89
Three month	62	68	75
Six month	51	76	83

*Denominator excludes subjects who reported zero episodes in follow-up, since the proportion of episodes that were AF cannot be calculated among such subjects.

7.4.4 Episode Reduction

At baseline, subjects who completed six months of follow-up experienced a mean of 9.5 episodes of symptomatic AF per month (Table 46). At three and six months, symptomatic AF episode counts were reduced to 3.7 and 3.4 episodes per month; the mean per-subject six-month reduction in symptomatic AF episode counts was 62.3% ($p<.0001$, paired t test). The 95% confidence interval for the percent episode reduction was 50.6 – 73.1. Figure 8 shows a per-subject plot of baseline and six-month symptomatic AF episode counts.

Table 46. Mean baseline, 3-month, and 6-month symptomatic AF episode counts, and six-month percent reduction in symptomatic AF episodes.

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

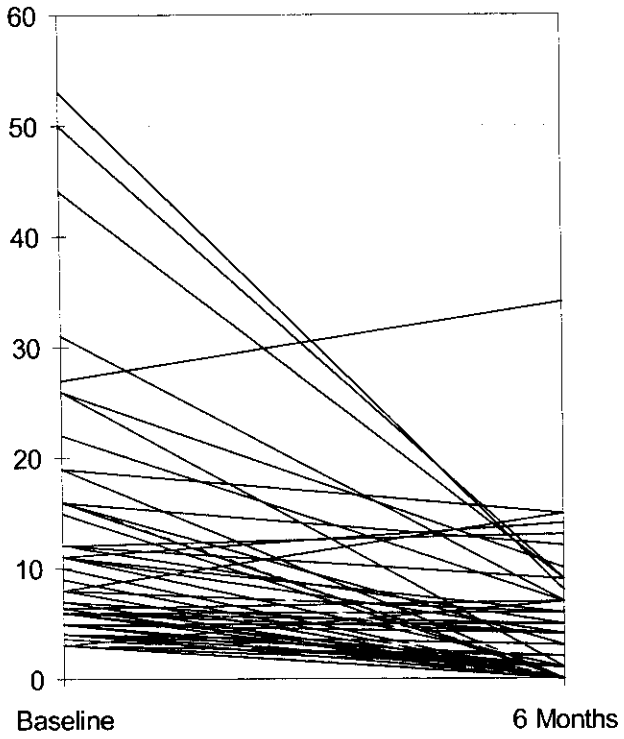


Figure 8. Per-subject plot of change in episode count from baseline to six months (N=77).

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

7.4.5 Target-Level Symptom Reduction

As per the Protocol, reductions in symptomatic AF episode counts were categorized as meeting or not meeting the target-level decrease according to the baseline number of episodes experienced. To be considered a success, subjects with three or four

episodes at baseline needed to experience a reduction of 75% or more during the six-month monitoring period, and subjects with five or more episodes at baseline needed to experience a reduction of 50% or more.

In all, 47 of 84 (56%) subjects in the effectiveness cohort achieved the target level decrease. Among the seven subjects with no six-month transmissions, two were also considered clinical successes (see Table 44), as manifested by verbal comments and marked improvements in AFSS episode frequency score. Including these two subjects as successes, the overall success rate was 49 in 84 (58%, 95% CI 48 - 68%). The width of the confidence intervals (± 10%) is in accord with the study Protocol's sample size calculation. Note that, but for the two noted exceptions, all success rate calculations consider those with zero six-month transmissions to be failures. Among the 49 successes, 14 occurred among 29 subjects with 3 to 4 episodes at baseline and 35 occurred among 55 subjects with five or more episodes at baseline (Table 47).

Table 47. Target-level episode reduction by baseline episode counts.

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

Abbreviation: s = successes, n = number of subjects in subgroup

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

Table 48 provides a summary of the six-month symptomatic episode reduction in the REVELATION® Tx investigations. The mean reduction in episode counts was 62%, with 79% of subjects having lower episode counts at six months of follow-up compared to baseline. Fifty-eight percent achieved the target level reduction, and over one-third of the subjects (35%) were episode free.

Table 48. Summary of six-month symptomatic AF episode reductions from baseline (N=84).

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

[a] Excludes 7 non-compliant subjects; b) includes two subjects with marked improvements on AFSS question 5

7.4.6 Predictors of Successful Episode Reduction

Several baseline subject (Table 49) and procedure (Table 50) characteristics were evaluated in exploratory analyses to determine whether these characteristics predicted target-level reductions in symptomatic AF episodes at six months. Only two differences in success rates, both paradoxical, were found:

- EKG at the time of the procedure: paradoxically, subjects in AF at the time of the procedure were more likely to show success at six months in episode reductions (Fisher's exact test, p = .009)
- Bidirectional conduction block (BDC): paradoxically, subjects for whom BDC could not be demonstrated were more likely to show long-term success (Fisher's exact test, p = 0.005)

Note that the study was not designed with sufficient power for subgroup analyses. The paradoxical results highlight the limitations of such analyses.

Table 49. Target-level reduction in episodes by subject characteristics (N = 84).

Characteristic	s/n	% Success
Age (years)		
< 50	12/23	52.2
≥ 50	37/62	59.7
Gender		
Male	38/66	57.6
Female	11/18	61.1
Previous RF Ablation		
Yes	16/27	59.3
No	33/57	57.9
Baseline Symptomatic AF Episodes		
3 to 4	14/29	48.3
5 to 9	18/31	58.1
10 to 14	5/9	55.6
15 to 19	5/7	71.4
> 20	7/8	87.5
EKG at Time of Procedure		
NSR	26/49	53.1
AF	19/24	79.2
Other	4/11	36.4
NYHA at Baseline*		
I	37/63	58.7
II	12/20	60.0

*Value missing in one subject
s = target-level reduction in symptomatic AF episodes; n = number of subjects in subgroup

Table 50. Target-level reduction in episodes by procedure characteristics (N = 84).

Characteristic	s/n	% Success
Procedure Date		
Aug 2000 – Sep 2001	12/22	54.5
Sep 2001 – Sep 2002	21/37	56.8
Sep 2002 – present	17/25	68.0
Isthmus Catheter*		
NAVABLATOR®	24/41	58.5
NAVABLATOR® then Other	11/18	61.1
REVELATION Tx®	7/8	87.5
REVELATION Tx® then NAVABLATOR®	1/2	50.0
REVELATION Tx®, NAVABLATOR®, then Other	1/2	50.0
Other	1/3	33.3
Bidirectional conduction block at procedure*		
Yes	33/61	54.1
No	14/15	93.3

*5 subjects did not undergo isthmus ablation since it had been performed prior to study enrollment. s = target-level reduction in symptomatic AF episodes; n = number of subjects in subgroup

7.4.7 Sensitivity Analysis

A sensitivity analysis was conducted to address the Agency's concern that the study did not use a method to determine whether symptomatic episodes reported by the subject represented discrete episodes of AF. Note that the focus of the study was symptomatic episodes of AF, which can only be reported by study subjects themselves, and did not focus on AF burden, the proportion of time spent in AF (independent of symptoms). In addition, all recorded episodes were reviewed by the monitoring service's independent cardiologist, who determined whether the rhythm associated with the symptomatic episodes was AF or not. No published studies of catheter ablation for AF have used or proposed any particular method to determine whether episodes reported by subjects represented discrete episodes of AF. Nearly all published studies use either cardiac event monitors or patient self-report.

In theory, subjects in our study may have recorded duplicate episodes of symptomatic AF during a single underlying "run" of AF. If this phenomenon occurred more at

baseline than follow-up, the resulting device effectiveness calculation could be overestimated. To address this concern for potential bias, a sensitivity analysis was performed, in which the proportion of subjects achieving the target-level decrease in symptomatic AF episode count at six months was calculated after assuming that an episode reported "soon after" a previous episode might, due to close proximity, represent duplicate reporting of the same underlying "run" of AF. For the purposes of analysis, "soon after" was defined as either within 1 hour, 6 hours, 12 hours or 24 hours of the initial episode. By definition, this analysis assumes that the subject is able to distinguish when he or she felt worse (episode started) but not better (episode ended).

Table 51 shows the results of this sensitivity analysis and the percentages of subjects achieving target-level reductions in symptomatic AF episodes at six months resulting from application of minimum times between episodes deemed to represent duplicate recordings. Overall, there was no apparent effect of the application of these constraints on success rates. Notably, no subject with a target-level of AF episode reduction reported an episode of symptomatic AF that occurred within one hour of the previous episode; thus, eliminating such reported symptomatic episodes as potentially representing the same underlying "run" of AF did not affect estimated success rates. In all, the analysis showed that two subjects would not have experienced the target-level decrease in episodes; one when eliminating episodes occurring between one and six hours of each other and another when eliminating episodes occurring between 6 and 24 hours of each other. Eliminating an episode of symptomatic AF occurring six or more hours after a previously reported episode as representing "duplicate" reporting of the same underlying run of AF is questionable. The results of this sensitivity analysis show that the potential effect of "overreporting" on the overall success rate would, if it actually occurred, have been negligible.

Table 51. Effect of "overreporting" on six-month success rates.

Minimum time between distinct episodes (hours)	Success Rate	
	s/n	%
0 (baseline)	47/84	56.0
1	47/84	56.0
6	46/80	57.5
12	46/80	57.5
24	45/80	56.3

Assumes 7 non compliant subjects are failures but would not have been affected by alternative definitions for episode counts. N decreased by four since elimination of the second episode at baseline would have disqualified these subjects.

7.4.8 Pacemaker Placements

Of 93 subjects undergoing RF ablation procedures, six had pacemakers present prior to ablation. (Note that the presence of pacemakers was not an exclusion criterion for the investigations.) A total of 16 subjects in the procedure cohort had pacemakers placed at some point during follow-up after RF ablation. As reviewed in the Protocol description, pacemaker placements were distinguished by both the indication for pacemaker placement and accompanying procedures, the time from ablation to pacemaker placement, and the expected impact of the pacemaker placement on symptomatic AF episode count reduction.

7.4.8.1 Pacemaker Placement plus AV Node Ablation

Ten subjects underwent AV node ablation and had pacemakers placed; four were placed after the six-month study visit and six before the six-month study visit (Table 52). Of these, three had target-level decreases in symptomatic AF episodes reported at six months. Episode reductions in these subjects are likely to be attributable to the reduced sensation of AF after AV node ablation; thus they do not contribute to the clinical (patient) success outcome. However, one subject [redacted] was considered a catheter ablation success at six months since the AV node ablation took place after the six-month visit.

7.4.8.2 Pacemaker Placement without AV Node Ablation

Six subjects underwent pacemaker placement in follow-up but did not undergo AV node ablation (Table 53). Of these, four achieved target-level decreases in episode counts during the six-month monitoring period (described below). Three underwent placement of pacemakers before the six-month endpoint and one more than one year after linear ablation. As discussed in the Protocol summary, evidence supporting a reduction in symptomatic AF episodes by pacemakers is controversial and lacking. Therefore, from the perspective of the six-month outcome, these subjects were considered successes. In one subject propafenone was also started (see section on AAD Changes).

. This 74-year-old man had a history of tachy-brady syndrome prior to RF ablation. He reported five episodes of symptomatic AF during the baseline monitoring period and one episode during the six-month monitoring period (with two additional compulsory weekly recordings). One-month rhythm strips reported as part of the study showed asymptomatic 2.5-second pauses and bradycardia. Beta-blockers were stopped and Holter monitoring showed continued bradycardia. As a Sponsor-approved protocol deviation, the subject completed the six-month study visit a few weeks early and subsequently underwent DDD pacemaker placement for tachy-brady syndrome.

This 71-year-old man reported 31 symptomatic AF episodes during the baseline period and seven during the six-month follow-up period. At the 12-month visit, he reported no AF recurrence. During the thirteenth month of follow-up the subject went into persistent symptomatic AF. Four-hundred thirty-six days after catheter RF ablation, the subject underwent pacemaker and internal cardiodefibrillator implantation with AF treatment algorithms. The investigator reported that this device placement was unrelated to linear ablation.

This 53-year-old man reported four symptomatic AF episodes during the baseline period and zero during the six-month follow-up period. Eight days after catheter RF ablation, the subject had episodes of paroxysmal AF as well as sinus node dysfunction attributed to ablation resulting in isolation of the sinus node. He underwent DDD pacemaker placement with defibrillator eight days after the RF ablation procedure for sinus bradycardia. The subject was also started on propafenone in follow-up. The decrease in six-month episodes might be attributable to the combined effect of RF ablation, pacemaker and new medication.

This 60-year-old man reported six symptomatic AF episodes during the baseline period and zero during the six-month follow-up period (with five compulsory weekly transmissions). In the second month of follow-up, despite flecainide treatment (a new AAD), he reported continued AF episodes. At day 69 after ablation, he underwent placement of a pacemaker with "atrial fibrillation suppression capability."

In summary, of the subjects who underwent pacemaker placement without AV node ablation, four achieved target-level decreases in symptomatic AF episodes at six

months. Of these four decreases, three were mostly likely attributable to linear RF ablation while one was probably attributable to the combined effect of ablation, medication and pacemaker/defibrillator (see below for complete description of AAD regimen changes).

Table 52. Summary of subjects who underwent pacemaker placement in follow-up with AV node ablation.

Target-level Decrease in Episodes	Subject ID	Implant Type	Days from ablation to PM placement	Comment	Considered success	Episode count (baseline/6 mo)
No		Pending	656	Recurrent AF, not controlled	No	3 / 3
		DDD	10	Sick sinus syndrome noted pre-procedure. Symptomatic pauses 9 days after procedure. Underwent DDD. Subsequent worsening of AF requiring AV node ablation at 12 months		11 / 6
		DDD	128	AVN ablation + DDD for progressive AF. Did not transmit six month rhythm strips		4 / -[b]
		VVIR	243	AVN ablation + PM at 8 months for chronic AF.		10 / -[b]
		VVIR	81	Developed atrial flutter then persistent AF, had AVN + VVIR at 3 months		6 / -[a]
		DDDR	122	Switched physicians due to insurance issue. AVN + DDD at 4 months. Did not record six-month episodes		10 / -[a]
		DDDR	251	DDDR at 8 months followed by AVN ablation at 10 months		4 / 3
Yes		DDDR	67	Recurrent AF, not controlled	No	7 / 0
		VVIR	190	AVN ablation + AV seq PM for recurrent AF after six-month visit	Yes	12 / 5
		DDDR	168	Sinus brady at follow-up, then worsened symptoms. Had AVN ablation + DDDR just before 6-mo follow-up	No	22 / 7

a) withdrew before 6 months; b) noncompliant with episode monitoring

Table 53. Summary of subjects who underwent pacemaker placement in follow-up without AV node ablation.

Target-level Decrease in Episodes	Subject ID	Implant Type	Days from ablation to PM placement	Comment	Considered success	Episode count (baseline/6 mo)
No		DDDR/ICD	129	AVB/NSVT seen on Holter at 3 mo. DDD DR with atrial pacing capabilities placed at 5 months. NSVT attributed to dofetilide ADE.	No	3 / 1
		DDDR	1	DDDR placed 1 day after procedure due to sinus arrest and 3-sec pauses noted in hospital. Pauses not attributed to ablation.		6 / 6
Yes		DDD	134	Tachy-brady syndrome present prior to ablation. Developed asymptomatic bradycardia + 2-second pauses at 6 weeks. Pacemaker placed for treatment of pauses.	Yes	5 / 1
		DDD/ICD	426	Continued/worsened AF at one year. DDD with atrial pacing capabilities placed at 1.2 years		31 / 7
		DDD/ICD	8	DDD/ICD at 8 days due to "sinus node dysfunction" attributed to isolation of SA node. Also started on propafenone		4 / 0
		DDD with pacing capability	69	Continued AF after ablation		6 / 0

131

Discussion. Pacemakers were placed in 16 of 93 subjects in the procedure cohort, raising two important questions: 1) Was the incidence of pacemaker placement higher than expected? and 2) Did placement of pacemakers interfere with interpretation of REVELATION® Tx effectiveness?

Incidence of pacemaker placement not high. Pacemaker placement is common in the treatment history of AF, especially in patients with refractory disease. Patients with AF often have underlying cardiac conduction disease, such as tachy-brady syndrome, for which pacemakers are often placed. Second, advanced pacemaker capabilities are currently under study as potential treatments for AF. The overall observed rate of pacemaker placement in this study was consistent with expectations in this patient population. Only one subject underwent pacemaker placement as a complication of RF ablation. The remaining subjects all had standard indications for pacemaker placement . Importantly, but for one case, pacemaker placement did not represent an adverse event or a result of a procedure-related complication. Rather, in 10 of 16 cases AV node ablation plus pacemaker placement represented an acknowledgment that response to treatment with REVELATION® Tx insufficiently controlled the subject's bothersome symptomatic AF episodes. In four of the remaining six cases, pacemaker placement was aimed primarily at treating the underlying bradycardia.

Effectiveness of pacemakers in symptomatic AF episode reduction not demonstrated. Episode reduction after AV node ablation is expected as a result of decreased conduction of rapid atrial firing through the AV node. Episode reductions in these subjects cannot be considered to represent a linear catheter ablation success. Of the six subjects who underwent pacemaker placement <u>without</u> AV node ablation, review of case histories as well as the published medical literature suggested that four could be considered successes, and the success was attributable to linear catheter ablation procedure, not pacemaker placement. Of these, one also received a new AAD (propafenone), after having failed sotalol, dofetilide, atenolol and flecainide; his response is probably also attributable to linear catheter RF ablation.

7.4.9 AAD Regimen Changes

The Protocol required that subjects continue antiarrhythmic drugs (AADs) after RF ablation. The Protocol also defined an alternative "clinical (patient) success" outcome as a target-level decrease in symptomatic AF episodes "while maintained on the same anti-arrhythmic drug regimen or a reduced dosage." As reviewed in the Protocol description, a classification system based on review of the right- and left-atrial catheter ablation literature was used to score changes in AADs occurring in subjects enrolled in the REVELATION® Tx clinical investigations. AAD changes occurring in all subjects over the entire 24 months of the study are reviewed in the section entitled "Long-term Follow-up." In this section, AAD regimen changes among the 49 subjects who achieved target-level reductions in symptomatic AF episode counts at six months are described. (Note that AAD changes among subjects who did not achieve target-level decreases in symptomatic AF episodes are not relevant to the clinical success.)

Table 54 shows AAD regimen changes in 49 subjects who achieved target-level reductions in symptomatic AF episodes at six months. These AAD regimen changes are detailed below.

Table 54. Summary of AAD regimen changes among 49 subjects with target-level decreases in symptomatic AF episodes at six months.

AAD Regimen Change	Frequency
Rate control only	1
Decrease	22
Increase	3
New AAD	12
Previous	1
Same	10
Total	**49**

New AADs. Of the 49 subjects with target-level decreases in symptomatic AF episode counts, 12 started a new AAD: two started amiodarone, six started flecainide, two started propafenone, one started disopyramide, and one started dofetilide. Reasons for starting the new AAD were not collected; it is possible they were started

in an attempt to boost the observed clinical response to linear catheter ablation. Of these 12 subjects, one is discussed below. This subject was considered to have clearly met the clinical (patient) success outcome.

> This subject reported 19 episodes at baseline, 0 at the three month visit (with 4 compulsory weekly strips during the three-month monitoring period) and 0 at the six-month visit (again with four compulsory weekly strips). Amiodarone was started prior to the six-month visit for unknown reasons. The decrease observed during the three-month monitoring period occurred prior to starting the new AAD and was attributed primarily to a catheter RF ablation effect.

Drug to which previous refractory. One subject started amiodarone, a drug to which he had been previously refractory.

Rate control. In one subject metoprolol (50 – 75 mg BID) was added to digoxin and flecainide. The ACC guidelines do not strongly promote beta-blockers to reduce recurrence of AF and a recent review notes has not found them to be effective.[75]

Increase. Three subjects had increases in the doses only of the same regimen used at baseline. As reviewed below, all three subjects had changes in symptomatic AF episode counts that appeared to occur independent of the AAD dose changes and thus can be considered catheter ablation successes.

> This subject recorded 26 symptomatic episodes at baseline, 0 during the three-month monitoring period (with six compulsory weekly strips) and 0 during the six-month monitoring period (with five compulsory weekly strips). The AAD regimen changed from amiodarone 200 mg QD plus digoxin 0.125 mg QD to amiodarone 300 mg QD plus the same dose of digoxin at the three-month study visit. The 100% decrease in episodes occurred before the AAD medication dose increase.

> This subject recorded 10 symptomatic AF episodes at baseline, one during the three-month monitoring period (with 3 compulsory weekly strips) and zero during the six-month monitoring period (with 5 compulsory weekly strips). His AAD regimen changed from Sotalol 160 mg BID to 200 mg BID; the change took place after the three-month visit. The subject showed a 90% reduction in episodes during the three-month monitroing period (prior to the sotalol dose increase) and a 100% reduction at six months. It is highly unlikely that these changes were related to the dose increase.

> This subject recorded 53 episodes of symptomatic AF at baseline, and 15 and 8 episodes of symptomatic AF during the three- and six-month monitoring periods, respectively. His AAD regimen change was an increase of amiodarone from 200 mg QD to 200 mg BID. The change took place after the three month study visit. This subject showed a 72% reduction in episodes prior to the dose increase and a 85% reduction by six months. The observed reductions were attributed primarily to linear catheter ablation.

Same or decrease. Thirty-two subjects had the same or decreased AAD regimen at follow-up.

In summary, three subjects had AAD increases and 12 started new AADs. Of the three with increases, all had target-level decreases in symptomatic AF episode frequency that occurred prior to of the dose increase and were therefore considered to have met the clinical (patient) success outcome. Of the 12 with new AADs, one had a target-level decrease in symptomatic AF episode counts prior to the new AAD and was therefore considered an ablation success.

A summary of the "clinical (patient) success" outcome should take into account both AAD changes and AV node ablations with pacemaker placement. This is discussed in the next section.

7.4.10 AAD Regimen Changes and Pacemaker Placement

Table 55 summarizes the experience of the 49 subjects with target-level decreases in AF episodes at six months with respect to both AAD changes and pacemaker placement.

Of the 49 subjects who achieved target-level decreases in AF episodes at six months, four underwent pacemaker placement without AV node ablation. Of these, a new AAD (propafenone) was started in one subject two weeks after the procedure. The remaining three experienced either a decrease in the AAD regimen (two subjects) or the same AAD regimen (one subject).

Of the three subjects who underwent AV node ablation plus pacemaker placement, one occurred after the six-month visit and therefore was considered a six-month success.

Of the 11 subjects in which a new AAD was started but a pacemaker was not placed, one subject described above) experienced a target-level decrease in symptomatic AF episode counts prior to the new AAD and was therefore considered a clinical success. The remaining 10 had reductions in episode counts that occurred in the setting of co-treatment with a new AAD.

Table 55. Summary of pacemaker and AAD changes during follow-up among 49 subjects who achieved target-level decreases in symptomatic AF episode counts.

	No Pacemaker Placement	Pacemaker Placement without AV Node Ablation				Pacemaker Placement with AV Node Ablation		
		Days from Procedure to PM				Days from Procedure to PM		
	-	8	69	134	426	67	168	190
AAD Change								
Rate Control only	**1**	-	-	-	-	-	-	-
Decrease	**17**	-	**1**	**1**	-	1	1	**1**[c]
Increase	**3**[a]	-	-	-	-	-	-	-
New AAD	10/**1**[b]	1	-	-	-	-	-	-
Previous	**1**	-	-	-	-	-	-	-
Same	**9**	-	-	-	**1**	-	-	-

Values in bold are considered to have experienced "clinical (patient) success," i.e., a target-level response without an increase in the AAD regimen. Notes: a) all three subjects considered clinical successes (see above), b) one subject (1009) with new AAD considered clinical success, c) PM placed after six-month study visit. Abbreviations: PM: pacemaker.

136

In summary, of 49 subjects with target-level decreases in symptomatic AF episode counts, 11 had concurrent treatment with a new AAD and an additional two had reductions that were likely to be affected by AV node ablation reducing the ability to detect episodes. The remaining 36 had reductions that occurred without an increase in AAD regimen or with AAD regimen changes that were either 1) highly unlikely to explain the observed reduction in episode count, or 2) represented the reinitiation of an AAD to which the subject had been previously refractory.

Table 56 provides success rates based on different assumptions about the effectiveness of the new AAD in these subjects with drug-refractory AF. Overall "clinical (patient) success" rates varied from 43 to 56%.

Table 56. Approach for interpretation of AAD regimen changes.

Approach	Assumption	Success Rate[a] (s/n, %)
1. Drug-refractory	Subjects are drug-refractory. The new AAD was unlikely to cause a clinically substantial decrease in episode count by itself. Attribute the episode reduction to catheter RF ablation.	47/84 (56.0%)
2. Not drug refractory	Despite non-response to 2 or more drugs prior to enrollment, subjects are not really drug-refractory. The new AAD caused most of the target-level reduction in symptomatic episode counts. Attribute the decrease to the new AAD.	36/84 (42.9%)
3. Uninterpretable	Effect confounded. One cannot tell whether effect due to AAD or linear catheter ablation. Exclude such subjects as "unevaluable."	36/73 (49.3%)

Notes: a) Excludes two subjects who achieved target-level symptomatic AF episode reduction but had AV node ablations and pacemakers placed within first six months of follow-up; includes three subjects as successes who had increases in AAD regimens that were preceded by target-level decreases in symptomatic AF episodes.

The Protocol specified two distinct definitions of success: 1) a reduction in symptomatic AF episodes of 50 or 75%, depending on the baseline number of episodes, and 2) "clinical (patient) success", defined as the same target-level reduction of symptomatic AF episode counts without other therapeutic maneuvers that might play a role in the observed success. Using the first outcome, the success rate was 58%. Using the second, stricter outcome, the success rate was 43% to 56%, depending upon one's assumptions regarding the effectiveness of new AADs to cause the target-level reduction in symptomatic AF episode counts in patients with drug-refractory paroxysmal AF. As reviewed in the Protocol summary, published medical data do not provide evidence to support a large, target-level response to additional AADs among the highly drug-refractory subjects in our clinical trial. In the absence of such evidence, the clinical (patient) success rate of 56% is clinically reasonable and probably represents the fairest assessment of the response to linear RF ablation in the

absence of other clinical maneuvers expected to meaningfully affect the occurrence rate of symptomatic AF.

7.5 *QUALITY OF LIFE*

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

7.5.1 Short Form-36

Changes in SF-36 scores suggested marked improvements in quality of life after treatment of paroxysmal AF with linear ablation using the REVELATION® Tx Microcatheter system (Table 57). Statistically significant improvements occurred in all but one ("general health") SF-36 dimension. The percentage of subjects who reported a clinically significant (≥ 10 points) improvement was between 30 and 55% for each dimension (Table 58), indicating a clinically important improvement in quality of life associated with the RF ablation procedure. Improvements were largest in vitality, social functioning, and bodily pain. Additionally, for these three scales and role emotional, the mean scores were improved from substantially below the US norms at baseline to the level of the US norms six months after ablation. Mean changes were clinically significant (≥10 points) in four of the eight categories.

Table 57. Baseline and 6-month SF-36 scores among 6-month completers.

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

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

Table 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

7.5.2 Atrial Fibrillation Severity Scale

The AFSS was employed to quantify subjects' perceptions of the quality of life burden due to symptomatic AF. At 6 months, AFSS scores showed substantial and significant improvements in episode frequency, duration and severity (Table 59). Fifty percent of subjects achieved an improvement of 10 or more points in reported episode frequency (Table 60). The main stated goal of linear RF ablation for AF was to reduce symptomatic AF episode frequency. However, the mechanism of action of RF ablation

140

in AF may also reduce episode duration and severity. As shown in Table 60, subjects who underwent RF ablation with REVELATION® Tx also showed clinically important reductions in episode duration (35%) and severity (49%).

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

Table 61 shows the relationship between the baseline number of symptomatic AF episodes recorded by event monitors and the frequency, duration and severity questions of the AFSS instrument. Baseline episode frequency was associated with AFSS frequency but not with duration or severity. Table 62 shows the relationship between the change in symptomatic AF episode counts from baseline to six months (i.e., the primary success outcome) and the change in the frequency, duration and severity subscales of the AFSS. Subjects who met the target-level reduction in AF episode counts recorded by event monitors also reported large increases in the AFSS frequency subscale. Additionally, subjects who reported target-level decreases in symptomatic AF episode counts also reported improvements in duration and severity of episodes.

Table 61. Relationship between baseline number of symptomatic AF episodes and AFSS frequency, duration and severity subscales (N=84).

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

Table 62. Change in symptomatic AF episode frequency and change in AFSS frequency, duration and severity subscales (N=77).

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

7.5.2.1 Symptoms Associated with AF Episodes

Symptoms typically associated with AF episodes decreased markedly and statistically significantly at three and six months after ablation compared to baseline (Table 63). At the six month visit, palpitations were reduced by 53% chest pain by 65%, shortness of breath by 45%, lightheadedness by 62% and fatigue/weakness by 54%. These findings corroborate episode reductions and quality of life changes described above.

Table 63. Symptoms associated with AF episodes by study visit.

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

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

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

7.6 *Other Six-Month Study Visit Findings*

In this section, other study visit findings are reviewed.

7.6.1 EKG Findings in Follow-up

Electrocardiograms were performed and read by study investigators at baseline, discharge and at one, three and six months of follow-up. Table 64 shows EKG findings at baseline and follow-up study visits. Normal sinus rhythm was present in 43% at baseline and 49% at six-months of follow-up. AF was present in 25% of subjects at baseline and in 21% at six months of follow-up.

Table 64. EKG findings at baseline and follow-up.

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

Freq: frequency

7.7 *COMPLICATIONS/ADVERSE EVENTS*

All adverse events experienced by study subjects were documented and have been appropriately reported. Adverse events were defined by the Protocol as a series of potential complications that could be expected in either cardiac catheterization or RF ablation. Site investigators were required to make a determination of whether the event was probably or possibly related to the device, or not related.

7.7.1 Serious Adverse Events

FDA defines[k] a major complication as an adverse event which "occurs within the first week following the investigational procedure and:

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

This description was used (p. 28 of Protocol) as the definition for a serious adverse event (SAE) throughout the REVELATION® Tx clinical investigations.

In the Phase III study, four SAEs occurred in three subjects during the first week after catheter ablation (see Table 65). The SAE rate was therefore 4 events in 95 procedures (4.2%). These three subjects are described in more detail in Table 66. Importantly, only one SAE was reported to be device-related. However, the study investigator did not indicate that the device had failed; rather it was thought that the device was used in a manner not consistent with the study Protocol's recommendations (i.e., technique related), resulting in SA node isolation. Detailed descriptions of SAEs are provided in Table 66.

[k] Appendix A. Recommended Clinical Study Design for Ventricular Tachycardia – Guidance for Industry and for FDA Reviewers. US Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiologic Health, May 7, 1999.

Table 65. Serious adverse events occurring within one week of linear catheter ablation.

				Relationship*	
Subject ID	**AE**	**Days from Procedure to SAE**	**Severity***	**To Procedure**	**To Device**
	Cardiac tamponade	0	Severe	Probably	Not related
	SA block requiring a permanent pacemaker + pneumonia	1 to 4	Moderate	SA block: Probably	SA block: Probably
				Pneumonia: Probably	Pneumonia: Not related
	Femoral arteriovenous fistula	1	Moderate	Probably	Not related

*Severity and relationship judged by investigator

Table 66. Detailed description of SAEs associated with REVELATION® Tx catheter ablation procedure.

Two hours after the procedure, this 65-year old woman had nausea and became hemodynamically unstable. Echocardiogram showed pericardial tamponade – which was treated with vasoactive drugs and a surgical pericardial window. The subject was discharged in NSR. Symptoms related to this procedure resolved after hospital discharge. The investigator stated that the protocol required maintaining ACT too high.
After the procedure, this 53-year-old man experienced aspiration pneumonia, anxiety attacks, self-limited pericarditis with pericardial effusion and posterior thoracic skin burns from the grounding pad due to hypersensitive skin. Serial post-procedure echocardiograms demonstrated that the pericardial effusion resolved spontaneously. Episodes of paroxysmal AF occurred after the procedure, accompanied by sinus node dysfunction that may have arisen from placement of the RF lesions along the lateral right atrium near the sinus node, resulting in SA node isolation. Sinus node dysfunction persisted for a week, and the subject agreed to undergo adjunctive implantation of a Medtronic Gem III AT atrial pacemaker/ICD one week after the RF ablation procedure.
This 54-year-old woman had post-procedure left groin pain. Ultrasound showed a femoral arteriovenous fistula, which was treated conservatively. Six days after the procedure she developed increased groin pain at home, resulting from increased bleeding from the fistula. She underwent a surgical repair the next day. The investigator noted that the complication was related to cannulation of the femoral vein and not to the study catheter.

146

7.7.1.1 *Serious Adverse Events More than One Week From Procedure*

Serious adverse events meeting all but the timing criterion of the SAE definition above occurred in three Phase III subjects at two study sites (Table 67). None of these were events related to the procedure or device. Two of these were related to pacemaker problems only. None was unexpected given the patient population recruited. It was unclear why the elective hospitalization for pulmonary vein ablation in subject 603 was reported as an SAE.

Table 67. Serious adverse events in REVELATION® Tx investigations occurring more than one week after linear catheter ablation.

				Relationship*	
Subject ID	**AE**	**Days from Procedure to SAE**	**Severity***	**To Procedure**	**To Device**
	Subject underwent atrial flutter ablation January 2003 (see below), ~580 days after linear ablation, followed by pulmonary vein ablation March 20, 2003 for recurrent AF (reported as SAE), 659 days after linear ablation	656	Moderate	Not related	Not related
	Near syncope attributed to pacemaker reverting to VVI mode at rate of 65 bpm; underwent emergent pacemaker generator change July 2002	232	Moderate	Not related	Not related
	Admitted to hospital for replacement of ventricular leads to initiate cardiac resynchronization therapy for progressive, non-ischemic cardiomyopathy	167	Moderate	Not related	Not related

*Severity and relationship judged by investigator

7.7.2 Adverse Events

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

Table 68 shows all adverse events thought by site investigators to be possibly or probably related to the procedure. Overall, twenty events were probably related to the procedure. Table 69 provides more detail on these subjects.

Table 68. Frequency of adverse events and relationship to procedure.

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

Table 69. Frequency of adverse events judged to be probably related to procedure.

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

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

Table 70 shows four adverse events reported by investigators to be possibly or probably related to the study device.

Table 70. Frequency of adverse events and relationship to device.

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

*previously described

149

The one "probably" device-related event in Phase III was described above (post-procedure pacemaker placement). The remaining five "possibly" device-related events in Phase III were as follows:

- Subject described previously with post-procedure pericarditis and pneumonia.
- Subject with undiagnosed inspiratory chest pain, treated with ibuprofen. No evidence of pulmonary embolism or pericarditis.
- Subject hospitalized one month after linear ablation for recurrent AF. A low INR measurement was observed, which was attributed to a drug reaction (sotalol). It is unclear why this adverse event was judged to be possibly related to the device.
- Subject hospitalized 111 days after linear ablation for AV node ablation plus pacemaker placement. This ablation was aborted and reattempted successfully two weeks later. It is unclear why this was reported as an AE related to the study device.

A complete listing of all reported adverse events (AEs) judged by investigators to be possibly or probably related to the device or procedure is presented in Appendix F.

Discussion. The published literature was reviewed in order to place the observed AE rate in the current investigations into perspective. The literature on right- and left-sided ablation has grown steadily over the past few years. Table 71 summarizes publications of RF ablation for various common arrhythmias, including three small studies on right atrial linear lesions for treatment of AF and other indications. All studies reported complications sparsely, if at all, but those complications reported are significant in both type and frequency, ranging from 8.3% to 22.2%, involving primarily phrenic nerve injury and sinus node injury. It should be noted that these articles may be reporting complications without regard for the FDA definition of "major complication."

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

Table 71. Published Complication Rates for Radiofrequency Catheter Ablation (RFCA) in the Right Atrium.

Reference	N	Complications (%)													
		Complete AV Block	Valve Damage	Coron. Artery injury/occl	Tamponade	Pericarditis	Pneumothorax	Venous Thrombosis	Pulmonary Emboli	Arterial Thrombosis	CVA/TIA	Bleeding at Puncture	Myocardial Infarction	Other	Death
Atrial Fibrillation (treated with linear lesions for RA compartmentalization or a RA'MAZE' procedure)															
Gaita et al., *Atrial mapping and radiofrequency catheter ablation in patients with idiopathic atrial fibrillation. Circulation 1998;97*	16	No complications reported													
Natale et al., *Catheter ablation approach on the right side only for paroxysmal AF. PACE 2000;23.*	18	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	§16.6 ¥ 22.2	NR
Garg, et al., *Right Atrial Compartmentalization Using Radiofrequency Catheter Ablation of Management of Patients with Refractory AF. J Cardiovasc Electrophysiol, 1999;10*	12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	§8.3	0.0
RFCA for Paroxysmal Atrial Fibrillation															
REVELATION Ablation System Study	**95**	**0.0**	**0.0**	**0.0**	**0.01**	**0.02**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.01**	**0.0**	**0.01**	**0.0**

NR=Not Reported NF=No Frequency Reported but these complications were noted NS=Not specific to the target arrhythmia but was reported for all arrhythmias collectively § = SA dysfunction ¥ = Phrenic Nerve Injury

* DVT

** AV Fistula=0.01%, not reported for any other procedure.

Reference	N	Complications (%)													
		Complete AV Block	Valve Damage	Coron. Artery injury/occl	Tamponade	Pericarditis	Pneumothorax	Venous Thrombosis	Pulmonary Emboli	Arterial Thrombosis	CVA/TIA	Bleeding at Puncture	Myocardial Infarction	Other	Death
Accessory Pathway															
Hindricks, et. al. *The Multicentre European Radiofrequency Survey (MERFS): Complications of RFCA of arrhythmias. European Heart Journal. 1993;14**	2222	0.63	0.05	0.0	0.72	NR	NR	0.18	0.09	0.18	0.49	0.32	NR	NR	0.13
Scheinman. *NASPE Survey on Catheter Ablation. Pacing Clin Electrop. 1995;18**	5427	0.17	0.11	0.06	0.13	NR	NR	NF	NF	0.0	0.15	0.06	NR	NR	0.08
Scheinman. *1998 NASPE prospective catheter ablation registry. Pacing Clin Electroph. 2000;23**	654	0.3	0.0	0.16	1.1	NR	NR	0.0	0.16	0.0	0.0	1.99	NR	NR	0.0
Calkins et al. *Catheter ablation of accessory pathways, av nodal reentrant tachycardia, and the av junction. Circulation 1999;99**	500	0.1	NS	0.2	NS	NR	NR	NS	NS	NS	0.2	NS	NR	NR	0.2

* Angkeow P. Calkins H., *Complications Associated with Radiofrequency Catheter Ablation of Cardiac Arrhythmias. Cardiology in Review 2001;9(3):121-130.* A review of 4 major reports, listed separately in this table and a selection of smaller studies specifically for RA RFCA for AF

NR=Not Reported NF=No Frequency Reported but these complications were noted NS=Not specific to the target arrhythmia but was reported for all arrhythmias collectively

AVNRT															
Hindricks, et. al. *The Multicentre European Radiofrequency Survey (MERFS): Complications of RFCA of arrhythmias. European Heart Journal. 1993;14**	815	5.07	NR	NR	0.24*	0.24*	0.0	1.11	0.24	NR	0.12	0.24	NR	NR	0.0
Scheinman. *NASPE Survey on Catheter Ablation. Pacing Clin Electrop. 1995;18**	5423	0.11	NR	NR	0.33*	0.33*	0.09	0.09	0.0	NR	0.00	0.06	NR	NR	0.0
Scheinman. *1998 NASPE prospective catheter ablation registry. Pacing Clin Electroph. 2000;23**	1197	0.74	NR	NR	0.0	0.0	0.08	0.08	0.08	NR	0.0	0.49	NR	NR	0.0
Calkins et al. *Catheter ablation of accessory pathways, av nodal reentrant tachycardia, and the av junction. Circulation 1999;29**	373	1.3	NR	NR	NS	NS	NS	NS	NS	NR	NS	NS	NR	NR	0.0

* Angkeow P. Calkins H., *Complications Associated with Radiofrequency Catheter Ablation of Cardiac Arrhythmias. Cardiology in Review 2001;9(3):121-130.* A review of 4 major reports, listed separately in this table and a selection of smaller studies specifically for RA RFCA for AF

NR=Not Reported NF=No Frequency Reported but these complications were noted NS=Not specific to the target arrhythmia but was reported for all arrhythmias collectively *=Reported as a combined complication (tamponade/pericarditis)

AV Junction															
Hindricks, et. al. *The Multicentre European Radiofrequency Survey (MERFS): Complications of RFCA of arrhythmias. European Heart Journal. 1993;148*	900	NR	0.11[f]	NR	NR	NR	NR	1.00	0.22	NR	0.0	0.0	0.0	NR	0.11
Scheinman. *NASPE Survey on Catheter Ablation. Pacing Clin Electrop. 1995;18**	2084	NR	0.0[f]	NR	NR	NR	NR	0.0	0.0	NR	0.1	0.0	0.05	NR	0.2
Scheinman. *1998 NASPE prospective catheter ablation registry. Pacing Clin Electroph. 2000;23**	646	NR	0.15[f]	NR	NR	NR	NR	0.0	0.0	NR	0.0	0.30	0.0	NR	0.15

Calkins et al. *Catheter ablation of accessory pathways, av nodal reentrant tachycardia, and the av junction. Circulation 1999;29**	121	NR	NS	NR	NR	NR	NR	NS	0.82	NR	0.82	NS	0.0	NR	0.65

* Angkeow P. Calkins H., *Complications Associated with Radiofrequency Catheter Ablation of Cardiac Arrhythmias. Cardiology in Review 2001;9(3):121-130.* A review of 4 major reports, listed separately in this table and a selection of smaller studies specifically for RA RFCA for AF

NR=Not Reported NF=No Frequency Reported but these complications were noted NS=Not specific to the target arrhythmia but was reported for all arrhythmias collectively [f]=Reported here as Significant Tricuspid Regurgitation

Ventricular Tachycardia															
Hindricks, et. al. *The Multicentre European Radiofrequency Survey (MERFS): Complications of RFCA of arrhythmias. European Heart Journal. 1993;14**	320	0.31	NR	NR	0.63	NR	NR	NR	0.63	1.0	1.26	0.63	NR	0.63[§]	0.31
Scheinman. *NASPE Survey on Catheter Ablation. Pacing Clin Electrop. 1995;18**	844	0.12	NR	NR	0.71	NR	NR	NR	NR	0.12	NR	NR	NR	0.36	0.0
Scheinman. *1998 NASPE prospective catheter ablation registry. Pacing Clin Electroph. 2000;23**	201	NR	NR	NR	1.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	1.5
Calkins et al. *Catheter ablation of accessory pathways, av nodal reentrant tachycardia, and the av junction. Circulation 1999;29**	146	1.4	0.7	NR	2.7	NR	NR	NR	NR	NR	1.26	0.7	NR	NR	2.7

* Angkeow P. Calkins H., *Complications Associated with Radiofrequency Catheter Ablation of Cardiac Arrhythmias. Cardiology in Review 2001;9(3):121-130.* A review of 4 major reports, listed separately in this table and a selection of smaller studies specifically for RA RFCA for AF

NR=Not Reported § Peripheral embolism

7.8 LONG-TERM FOLLOW-UP

Long-term follow-up in the Phase III study included a twelve-month study visit and a 24-month telephone contact. The completeness of long-term follow-up in the REVELATION® Tx trials has been excellent (Table 72), with no subjects lost to follow-up and only three missed study visits. Eighty-eight Phase III subjects have completed six months of follow-up, 64 have completed 12 months of follow-up and 30 have completed 24 months of follow-up. Nine subjects who completed the 12-month visit in the last six months have data still pending at study sites. Two subjects missed three early study visits (Table 73) but have completed subsequent visits.

Table 72. Phase III study visits.

	Frequency
Visit Type	
Baseline	93
Discharge	93
1 Month	91
3 Month	89
6 Month	88
12 Month	64
Phone Contact	
24 month	30

Table 73. Missing Study Visits

Subject ID	Visit Missed	Comment
	3 month	Visit missed due to insurance reasons; all other visits occurred
	1 month, 3 month	6 month and 12 month have occurred

Subjects who withdrew from the Phase III investigations in long-term follow-up are listed in Table 74. Three (1403, 1414, 1811) withdrew before and one subject withdrew after (1804) six months due to non-study-related reasons. One subject (512) terminated early with Sponsor approval for placement of a pacemaker for sinus

pauses. Two (1601, 1614) withdrew, one at eight months, one at 81 days, for placement of a pacemaker.

Table 74. Details of subjects who withdrew from Phase III trial.

Terminated	Frequency	Subject ID	Comment	Last Study Visit
Voluntarily withdrawal prior to six months	3		Insurance change; Moved out of state; Anxiety/depression	3 month, 1 month, procedure
Early 6-month visit and study termination	1		Early termination for pacemaker placement without AV node ablation for asymptomatic pauses	6 month
Voluntarily withdrawal at six month visit	1		Pacemaker placed at 8 months	12 month
Therapeutic failure	1		Chronic AF, pacemaker placed at day 81	6 month
Voluntarily withdrawal after six month visit	1		Subject moved out of country, not followed after 6 month visit	6 month
Total	7			

7.8.1 Twelve Month Study Visit

The twelve-month study visit included a physical examination, an assessment of medications in use, a summary of arrhythmias experienced and hospitalizations or ER visits, and an assessment of adverse events. Provided below are statistical results for heart rate, blood pressure, weight, and NYHA status for baseline and all follow-up visits through 12 months based on physical exam.

7.8.1.1 Physical Examination

Mean heart rate (Table 75), blood pressure (Table 76) and weight (Table 77) showed no noteworthy changes over the study period. At twelve months, there was no remarkable deterioration of overall cardiac function, as measured by the New York Heart Association (NYHA) classification (Table 78).

Table 75. Heart rate by study visit.

	Resting HR (bpm)					
	N	Mean	SE	Min	Median	Max
Visit Type						
Baseline	86	70.3	1.8	45	68	124
Discharge	86	71.8	1.7	48	68	130
1 Month	83	70.2	1.6	48	70	117
3 Month	82	68.6	1.6	39	67	118
6 Month	83	70.6	1.7	46	68	134
12 Month	63	73.0	1.8	48	72	106

Table 76. Subject blood pressure at baseline and follow-up study visits.

	Resting Systolic BP (mmHg)			Resting Diastolic BP (mmHg)		
	N	Mean	SE	N	Mean	SE
Visit Type						
Baseline	86	128.3	2.0	86	75.7	1.2
Discharge	86	122.9	1.7	86	69.7	1.0
1 Month	84	124.9	1.5	84	75.8	1.0
3 Month	82	130.0	1.9	82	78.3	1.2
6 Month	81	125.5	1.7	81	76.0	1.1
12 Month	61	129.8	2.2	61	76.1	1.2

Table 77. Subject weight at baseline and follow-up study visits.

	Weight (lbs)					
	N	Mean	SE	Min	Median	Max
Visit Type						
Baseline	93	200.1	4.3	117	196	340
1 Month	87	199.0	4.5	116	196	328
3 Month	83	200.4	4.5	118	192	344
6 Month	81	202.4	4.5	119	200	344
12 Month	60	203.8	5.9	122	196	346

Table 78. New York Heart Association class at baseline and follow-up study visits.

	NYHA Classification								
			I		II		III		Total
	Freq	%	Freq	%	Freq	%	Freq	%	
Visit Type									
Baseline	-	-	64	74.4	22	25.6	-	-	86
1 Month	-	-	71	83.5	14	16.5	-	-	85
3 Month	-	-	67	79.8	16	19.0	1	1.2	84
6 Month	1	1.2	72	85.7	9	10.7	2	2.4	84
12 Month	-	-	50	79.4	12	19.0	1	1.6	63

Physical examination findings by category are shown in Table 79. There were no trends in the general, neurologic and respiratory categories. The study visit case report form asked for cardiac abnormalities on physical examination; however, many non-physical examination findings were entered into the form. Physicians often reported "atrial fibrillation" on physical examination (if the subject was in AF, the cardiac physical examination entry should be "irregularly irregular"). Therefore, the entries "AF" and "irregular" were assumed to represent possible AF. Note that the determination of whether a subject was in AF requires an EKG, which was not required at the twelve month visit. Table 80 shows details of the cardiac findings at the 12-month visit. Eighteen (28%) had "AF" or irregular heart rate. Table 81 shows the number of subjects with presumed atrial fibrillation, by the above physical examination definition, at study visits. At follow-up, irregular heart rhythms consistent with AF were noted in 11 to 27% of subjects. (See section entitled "EKG Findings in Follow-up" for review of EKG findings at baseline, discharge and one to six months of follow-up.)

Table 79. Physical examination findings by study visit.

Visit Type	Category							
	Cardiologic		General		Neurologic		Respiratory	
	a/N	%	a/N	%	a/N	%	a/N	%
Baseline	23/93	24.7	0/93	0	0/93	0	3/90	3.2
Discharge	14/93	15.1	1/92	1.1	-*	-	4/89	4.3
1 Month	21/90	23.3	0/90	0	1/88	1.1	1/89	1.1
3 Month	18/88	20.5	1/88	1.1	1/86	1.1	1/87	1.1
6 Month	18/88	20.5	1/87	1.1	3/84	3.4	2/86	2.3
12 Month	17/63	27.0	0/63	0	0/62	0	0/63	0

*Neurologic status not on discharge case report form; a = abnormal, N = number of subjects

Table 80. Details of cardiac examination findings at 12 months (N=64).

Findings	Frequency	%
AF or irregular	18	28.1
Tachycardia	1	1.6
Other	3	4.7
None	2	3.1

Table 81. Number of subjects with irregular HR or "AF" noted by study visit.

Study Visit	AF* Noted	Frequency	%
Baseline	18	93	19.4
Discharge	10	93	10.8
1 Month	17	91	18.7
3 Month	12	89	13.5
6 Month	16	88	18.2
12 Month	17	64	26.6

*AF as determined by "AF" or "irregular" in physical examination entry

7.8.2 24-Month Telephone Contact

At 24 months subjects were contacted by telephone and assessed for overall status, arrhythmia experience, medications and adverse events.

7.8.2.1 Symptomatic AF

As per the Protocol, at both the twelve-month study visit and the 24-month telephone contact, subjects estimated the number of symptomatic AF episodes experienced since the last study visit. Since rhythm strips were not recorded after six months post-ablation, it is unknown how many of these episodes had AF as the underlying rhythm. At twelve months, 26 (43%) reported no symptomatic episodes since the last study visit and 39 (77%) reported three or fewer episodes. At 24 months, 17 (63%) reported no symptomatic AF episodes since the last study visit and 19 (74%) reported three or fewer episodes. Normalized to a 30-day reporting period, the mean (median) number of monthly episodes at month 12 was 3.0 (1.0) and at month 24 was 7.1 (0.17). The twelve-month mean figure compares favorably with mean episode frequency reported at 6 months (3.7) and is less than 1/3 that reported at baseline (9.5).

Six subjects did not provide verbal reports of AF frequency experienced since the last study visit. One had undergone AV node ablation and was not expected to have symptomatic episodes. Review of associated case report forms and office visit notes showed two (who continued to show good responses, one subject in chronic AF and two with ongoing symptomatic AF (Table 82).

Table 82. Subjective outcomes among subjects not verbally reporting AF episodes experienced since prior visit at the 12 and 24-month visit/contact.

Subject identifier	Study Visit	Comment
1106	12 months	"Patient verbally reports that the frequency of palpitation is far less than before."
1813	12 months	AF "on going"
2304	12 months	Subject had undergone AV node ablation. Office visit notes stated that subject "…denies any syncope, ...dizziness, …palpitations…"
1009	24 months	"Continuous since 12/01"
1104	24 months	"…a few episodes of palpitations [over the prior 12 months]…"
1703	24 months	"Pt in chronic afib"

Table 83. Frequency of AF episodes reported since last study visit, standardized to 30 days.

AF Episodes Last 30 Days	Visit Type	
	Month 12 N=64	Month 24 N=30*
0	26	17
1	10	-
2	3	2
3	8	1
4	3	-
5	4	1
7	1	-
8	1	1
10	-	2
12	2	-
14	1	-
30	2	2
90	-	1

*Missing values in 3 each for 12 and 24-month visits, respectively

7.8.2.2 Hospitalizations and Emergency Room Visits

Eleven emergency room visits for cardiac arrhythmias occurred among eight subjects in follow-up, all for AF. In two visits, cardioversion was performed; in 4 visits medications were administered, and in 5 cases the subject was treated conservatively.

During follow-up, 34 hospitalizations occurred in 21 study subjects. Of these, 30 were specifically for arrhythmia, and 25 were for AF (Table 84). Of the 34 hospitalizations, 7 involved cardioversions and in 5 pacemakers were placed (previously described).

Table 84. Frequency of hospitalizations for cardiac arrhythmia noted since last study visit.

Visit Type	AF	Atrial Flutter	Other	Total
1 month	3	-	-	3
3 months	6	2	2	10
6 months	4	-	-	4
12 months	5	-	1	6
24 months	7	-	-	7
Total	**25**	**2**	**3**	**30**

7.8.2.3 Follow-up Ablations

Five subjects had a total of six non-AV node ablations that were not second linear ablation procedures (Table 85). All but one occurred after the six-month follow-up interval. One subject (underwent pulmonary vein ablation 67 days after the initial investigational procedure. Although this subject had a target-level decrease in symptomatic AF episodes during the six-month monitoring period compared to baseline, the reduction may have been attributable to pulmonary vein ablation; thus, in all data presented in this document, this subject has not been considered a right-atrial linear catheter ablation success.

Table 85. Non-AV node ablations occurring during follow-up.

Subject ID	Details
	Repeat right-atrial linear ablation 4/28/2003 for recurrent AF, 285 days after linear ablation
	Pulmonary vein ablation 9/24/2003 for recurrent AF, 707 days after linear ablation
	Right atrial ablation 9/15/2003, modification of right atrial quarter procedure and circumferential lesion around SVC, 728 days after linear ablation
	Atrial flutter ablation January 2003, ~580 days after linear ablation, followed by pulmonary vein ablation March 20, 2003 for recurrent AF, 659 after linear ablation
	Pulmonary vein ablation at 6/23/2003, 67 days after linear ablation

7.8.2.4 *Medications in Follow-up*

Table 86 shows AAD medication use at baseline and in follow-up by study visit. There were neither obvious trends in medication use at follow-up nor differences in AAD use between follow-up periods and baseline.

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

Discussion. Follow-up was complete in Phase III of the REVELATION® Tx clinical trial. No subjects have been lost to follow-up and only two subjects had missing visits. Physical examination showed no obvious trends in physical findings. At twelve months, physical examination findings showed no marked progression of disease. The frequency of AF episodes in follow-up, estimated by subject self-report, was substantially less at twelve months than at baseline. The twenty-four month follow-up was too small to permit comparisons. Hospitalizations and ER visits were relatively uncommon and did not show trends. Five subjects underwent subsequent

ablations; four of these were 280 days or more after initial linear ablation. Medication use in follow-up showed no obvious trends.

8 DISCUSSION

This PMA amendment reports results of a Phase III clinical investigation of right-atrial linear catheter ablation with the REVELATION® Tx Microcatheter system for the treatment of symptomatic paroxysmal AF. The clinical study, a non-randomized, single-arm clinical trial with a before-after design, showed that the creation of linear RF lesions using the study catheter system produced clinically important reductions in the frequency of symptomatic AF in the setting of an excellent safety profile.

Reductions in episode frequency at the six-month study endpoint were in the expected range given the lesion sets chosen, and were accompanied by improvements in quality of life as measured by both general and arrhythmia-specific instruments. The safety of the RF ablation was excellent, with an SAE rate that was compatible with other, commonly performed ablation procedures. Notably, since catheter ablation did not take place in the left atrium, there were no cases of stroke or pulmonary vein stenosis.

Catheter-based right-atrial RF ablation using a linear catheter represents a clinically valid and safe approach to symptomatic paroxysmal AF. As opposed to the "dot-to-dot" technique in common use today, the unique design of the REVELATION® Tx Microcatheter promotes the creation of continuous, transmural lesions, which may more closely reflect the lesions produced in the surgical "maze" procedure. Response rates observed in the clinical study were high enough to be clinically important, allowing a right-atrial approach to be a reasonable initial treatment strategy for symptomatic AF; it is especially relevant for physicians and patients who may wish to avoid the risk of pulmonary vein stenosis that has occurred in left-atrial procedures.

Section 7B: Excerpts of IDE submission

Choice of lesion set

G970280/S013

1. Email from Cardima to FDA reviewers dated 10/29/1998

Measurement of chronic effectiveness

G970280/S013

2. Email from Dr. Portnoy to Cardima dated 11/16/1998 regarding reporting bias
3. Informed consent document as submitted by Cardima

G970280/S021

4. FDA conditional approval letter dated 5/21/1999 including Item #5 regarding potential for over-reporting at baseline

G970280/S042

5. FDA letter dated 5/9/2001regarding patient non-compliance at follow-up

Non-investigational device use constitutes failure

G970280/S023

6. Meeting minutes from conference call of 5/19/1999

G970280/S035

7. FDA conditional approval letter dated 4/7/2000

G970280/S036

8. Meeting minutes from FDA-Cardima meeting dated 4/20/2000

G970280/S039

9. Email from FDA to Cardima dated 6/23/2000
10. Letter from Cardima dated 7/18/2000 acknowledging that non-investigational catheter use would render a subject a study failure

Acute procedural data

G970290/S013

11. Case report forms as submitted by Cardima for recording of the acute effectiveness for Revelation Tx

G970280/S027

12. Table of before and after pacing thresholds and electrogram amplitudes for Phase I and II patients

NavAblator

G970280/S034

13. Letter from sponsor dated 3/2/2000 stating that the NavAblator will be used with the Revelation Tx for treatment of AF

G970280/S054

14. Letter from Cardima dated 12/17/2002
15. Modified investigational protocol pages as submitted by Cardima

AAD use with respect to patient success

G970280/S047

16. Lead review memo dated 12/5/2001
17. Modified protocol pages as submitted by Cardima

Portnoy, Stuart

From: Jack Douglas [jack.douglas@cardima.com]
nt: Thursday, October 29, 1998 3:18 PM
: Stuart Portnoy, MD
Cc: Allan Abati; Dina Fleischer; Donna Bea Tillman; Barbara Zimmerman
Subject: re: Cardima AF Project

Dr Portnoy

In our conversation the other day, we touched on several subjects that we agreed warranted further discussion by your staff. I am sending this e-mail with copies to other group members that briefly highlights those topics.

Our system will consist of the REVELATION Tx System (formerly known as Pathfinder AFTC), the Radionics generator and Naviport deflectable guiding catheter.

Please note we have changed the product name. Is this an administrative issue?

Following on our successful feasibility trial, we intend to treat AF patients strictly in the right atrium, and will be sending a supplement to request an expanded multicenter study. To our knowledge there are no published EPS methods for pre-screening patients for this procedure solely in the right atrium, and we will include all patients with paroxysmal AF with at least 3 episodes/month. The final device labeling will clearly state the device is limited for ablation use on the right side.

We will pursue a reduction of AF episodes (with or without continued drug therapy) and quality of life enhancement as objectives. We plan to show the improvement for a period of six months post treatment for the pre-market approval application.

Although a recognized optimal lesion set for treating AF has not yet been defined in the literature, we have proposed a set of lesions for this trial, which should produce a Maze-like effect. The proposed set is based upon the success we saw in our European trial, which led to CE Mark certification, and the ten patient feasibility trial conducted in the U.S. Investigators will use this lesion set in order to maintain some consistency, yet slight deviations may occur based on best medical judgment which may be guided by mapping during the patient treatment. We would not want an occasional deviation to disqualify a patient.

We understand that the number of patients to be enrolled should be based on a statistical analysis based on safety and effectiveness. We understand that if the results show significant improvement, based on the endpoints of episodal reduction or/and enhanced quality of life, that it may be possible to submit a PMA based on interim results.

We would like to count enrolled patients as patients that sign a consent form and have an attempted treatment.

We plan to monitor episodes using cardiac event cards. Patient compliance will rely on proper patient orientation and training prior to enrollment in order to ensure compliance. We are interested in the FDA's opinion regarding the use of diaries. Is this a requirement, or recommendation, or have use of diaries been found to be unreliable? What is the agency's experience with use of loop recorders? Has use been found to be a reliable measure?

We want to agree upon these and other issues regarding our study prior to commencing; i.e. arrive at a satisfactory contractual agreement. It may also be important to get early panel member feedback on the study.

Thank you for taking your time to review these issues. We will be sending several supplements in the near future to report on our progress, as well as propose expansion to a pivotal study. Thus your timely feedback will be much appreciated.

Regards,

Jack Douglas

1. Radionics
2. RA only → quite eff, randomized? to what
   better if pts act as their own control.
3. endpoints look okay (↓ freq. episodes / QOL)
4. lesion set sounds good
5. Need full flu data on sample size (No interim stat analysis)
6. will need pre auth based on pts? (i.e. 6 mons)
7. Panel feedback / agreement may not be able?

64

Portnoy, Stuart

From: Portnoy, Stuart
nt: Monday, November 16, 1998 10:49 AM
: Jack Douglas (E-mail)
Cc: Fleischer, Dina J.; Zimmerman, Barbara C.; Tillman, Donna-Bea
Subject: Cardima REVELATION Right Atrial AF Ablation System

Dina, Barbara, Donna-Bea, and I met earlier this week to discuss the issues raised in your E-mail dated October 29, 1998 regarding your REVELATION Right Atrial AF Ablation System. The following are the recommendations that we have for you at this time:

1. Radionics RF Generator

   We are concerned that your investigational AF ablation system includes an RF generator which does not appear to be on a track for market-approval. Please further discuss this issue with Barbara Zimmerman.

2. Indication for Use

   Your intention to market your AF ablation system for use only in the right atrium appears acceptable. Your proposal to include in the final device labeling a Warning that clearly states that the device is limited for ablation only in the right atrium is appropriate and will be a necessary part of your Instructions for Use and device packaging labeling.

3. Clinical Trial Design

   We acknowledge that performing a randomized clinical trial to investigate AF ablation is probably not the best way to determine the safety and effectiveness of this procedure. Instead, we believe that the most appropriate study design is for patients to act as their own control. Consequently, your proposal to include as a primary study endpoint the demonstration of a reduction in AF episodes appears acceptable. Please note that to collect valid scientific evidence and minimize the potential for reporting bias, it will be necessary for you to design your clinical study so that patients are monitored for AF episodes for a certain period of time prior to receiving ablation therapy.

   We believe that you should consider including other primary study endpoints such as the rate of occurrence of major complications and patient deaths, and the acute non-inducibility of AF (or some other surrogate of acute success). Please note that although we believe that a certain quantitative improvement in patient quality of life is clinically relevant, demonstrating this improvement would most likely be considered a secondary endpoint of the study. Your proposal to follow patients for 6 months appears acceptable, but this period of time may ultimately depend on patients' frequency of reported AF episodes during the post-ablation period.

4. Lesion Set

   Your proposal to include in the investigational protocol a lesion set (which you believe is optimal) appears acceptable. We acknowledge that investigators will use this lesion set in order to maintain some consistency, yet slight deviations may occur based on best medical judgment which may be guided by mapping during the patient treatment. Such occasional deviations presumably will not disqualify patients from data analysis.

5. Interim Data Analysis

   We believe that it is inappropriate to submit a PMA application based on interim study results. Please note that the size of your PMA patient population should be consistent with your prospectively defined sample size. In addition, please note that prior to submitting your PMA application, it will be necessary for all treated patients to have been followed-up for frequency of AF recurrence out to the end of the chronic success monitoring period.

6. Event Monitoring

   Your proposal to monitor AF episodes using cardiac event cards is appropriate.

7. Contractual Agreement

   Please clarify what you mean my 'contractual agreement'. If you would like to arrange an Agreement Meeting per FDAMA, we would refer you to the guidance document "Early collaboration meetings under the FDA Modernization Act"."

   Please note that we plan to work closely with you prior to your multicenter study expansion to provide you with the guidance necessary to design what we believe would be a study intended to demonstrate the safety and effectiveness of an investigational AF ablation system.

   Since the Circulatory System Devices Panel met just last July to discuss AF ablation clinical trial design, we believe that obtaining further Panel input at this time would not be very helpful.

Sample Patient Informed Consent Form

Title of Project: "Evaluation of Radiofrequency (RF) Ablation of Atrial Fibrillation in the Right Atrium"

Protocol No.: (C97-103-AF, Phase IIB)

Principal Investigator: (_____)

BACKGROUND

I have been asked to participate in a research study to evaluate a new approach to the management of atrial fibrillation called radiofrequency catheter ablation. This involves the creation of multiple burn lines in the right atrium (the upper chamber of the heart) using a catheter placed into the heart through veins in my leg(s) and/or neck. The device to be evaluated during this study is the REVELATION™ Tx MicroCatheter System. The Sponsor of this study is Cardima, located in Fremont, California, USA.

I have been asked to participate in this study because I have atrial fibrillation that does not respond to or is difficult to control despite the use of medication.

This study is being conducted in up to fifteen centers in the United States and will involve approximately 80 participants. My participation in this study will involve additional follow-up clinical tests and examinations for a period of six months post procedure.

PURPOSE OF RESEARCH

The purpose of this research is to determine the safety and effectiveness of creating burn lines in my right atrium (upper chamber of the heart) using radiofrequency energy with the REVELATION™ Tx MicroCatheter System to treat my atrial fibrillation.

PROCEDURES

If I decide to participate, within 30 days prior to the procedure, I will have a complete physical examination, including a medical history. I will also undergo routine testing, including an electrocardiogram, a Masters Step Test (walking up and down 2 steps to determine my heart's response to exercise), a 24 hour Holter monitor (a continuous EKG monitor worn for 24 hours to record my heart rhythm), and laboratory tests (to check my blood clotting times). Approximately one teaspoon of blood will be withdrawn from a vein to check my blood clotting times. If I am a female and capable of becoming pregnant, an additional test will be performed within 24 hours prior to the procedure to determine if I am pregnant. If the test is positive, I will not be eligible to participate in this study.

I will also be given a cardiac event monitor (a small device about the size of a credit card) to record my heart rhythm both during short periods when I am experiencing heart symptoms. This small device is to be carried with me at all times. I will be instructed in its use and how to relay the information from the cardiac event monitor to a database by telephone. I understand to be eligible for this study, I must have at least three documented, transmitted episodes of symptomatic atrial fibrillation within a 30 day period.

If I am not already on Coumadin (a medication that "thins" my blood and is commonly prescribed for patients who have atrial fibrillation), I will be started on it at least four weeks prior to the procedure. My physician will obtain blood samples at his discretion to keep my blood thinned at a therapeutic level.

Periodically during my participation in this study, I will be asked to complete two Quality of Life questionnaires (the SF-36 and the Atrial Fibrillation Severity Scale). These questionnaires will take about twenty minutes of my time to complete. I will complete the questionnaires prior to the procedure (within the baseline period) and at the 3 and 6 month follow up visits after my procedure.

Within two days prior to the procedure, I will have a transesophageal echocardiogram (my heart function will be imaged with sound waves after I swallow a small tube) to check for abnormalities in my heart. The tube is removed immediately after the test is completed.

Three to four days prior to the procedure, I will stop taking my coumadin as my physician instructs. The day before I have the procedure, I will have an injection of low molecular weight heparin (another form of a blood thinner that is injected under the skin).

The night before the procedure, I will not eat or drink anything after midnight. I will arrive at the hospital at the time my physician tells me to. Approximately one hour prior to the procedure, I may be given medication to relax. I will then be brought to the Electrophysiology Lab where I may be given additional sedative medication. The procedure will last between approximately two and eight hours. During the procedure, I may be either asleep or be awake but feel sleepy and relaxed throughout the procedure.

During the procedure, a local anesthetic will be used so that catheters (long, thin tubes) may be placed in my heart through the veins in my legs and neck. Once the catheters are positioned, I will begin to receive heparin through an intravenous line. With the catheters in place, the rhythm of my heart will be studied in detail and recorded from several locations. Arrhythmias (irregular heart beats) may be induced (started) and pacing (sending signals from an external source via a catheter to alter my heart rate) may be performed. During this time, I may be aware of palpitations (rapid heart action). The REVELATION™ Tx catheter will be connected to a radiofrequency source to ablate (burn) tissue in the right atrium (upper chamber) of my heart. The REVELATION™ Tx will be placed through a special deflectable catheter to create at least one of the lines in my heart (this may help improve the contact between the REVELATION™ Tx catheter with my heart tissue) . It is hoped that this ablation will stop or reduce the atrial fibrillation that I currently experience. Periodically, additional specimens of blood will be taken from one of the catheters to test the clotting time of my blood.

At the end of the procedure, the heparin drip will be stopped so that the catheters can be removed from the veins in my legs and neck. I will be required to remain lying in bed for approximately six

hours to prevent bleeding from the catheter entry site. On the evening after the procedure, my coumadin medication will be resumed and I may be restarted on my heparin drip or may receive low molecular weight heparin. Additionally, I will be required to wear a continuous EKG monitor for a minimum of 24 hours. Another echocardiogram will be performed within 24 hours after the procedure. Before I am discharged from the hospital, I will be given my cardiac event recorder again.

I may be required to remain hospitalized at least overnight following the procedure.

Upon discharge from the hospital, I will be asked to return at specified intervals for follow up visits. I will be required to have my blood tested periodically to monitor the clotting time of my blood and make any necessary medication adjustments. I will continue to take my antiarrhythmia medications (the medications for controlling my heart rate) for a minimum of three months after the procedure, unless my physician instructs otherwise. I will be asked to continue carrying the cardiac event monitor with me at all times and to use the monitor as instructed for the six month follow up period.

Follow up exams are scheduled for Month 1, Month 3 and Month 6 after the procedure. At each of these visits, I will have a physical examination, an electrocardiogram, and a complete review of my medications and cardiac event monitor tracings At the Month 3 visit, I will be asked to perform the Masters' step test, to have a transthoracic echocardiogram, a Holter monitor and complete the Quality of Life questionnaires. At the Month 6 visit, I will have a Holter monitor and again complete the Quality of Life questionnaires. The purposes of these scheduled follow up visits is to determine if my atrial fibrillation recurs, to examine the pumping function of my heart, to collect safety data and to collect data on how the procedure may or may not have affected the quality of my life.

DISCOMFORTS

During this procedure, I may experience some discomfort. These discomforts include the following:

- I will not be permitted to eat or drink from midnight on the day of the procedure until after the procedure
- I will have multiple needle sticks in my veins to insert intravenous lines, catheters and to draw blood specimens. These sticks may cause a small amount of bleeding and/or bruising.
- I will have several EKGs performed. This involves cleaning and rubbing on several spots on my chest and the attachment of limb leads to my arms and legs.
- I will have multiple echocardiograms performed which involve lying still on my back and left side for approximately 20 minutes for each echocardiogram performed.
- I will experience discomfort from the administration of local anesthetic in my right and left groin and right neck at the start of the ablation procedure.
- I may experience bruising in my groin or neck after the procedure due to placement of catheters in these areas. This bruising may take several weeks to resolve.
- During the actual procedure and for six hours after the procedure, it will be necessary for me to lie flat on my back without sitting up.
- I may experience inconveniences related to clinical study participation and the requirement of 6 month follow-up.

RISKS

This procedure is considered to be experimental and as such, I need to be aware of possible complications accompanying cardiac electrophysiology and catheter ablation. Also, there may be some risks which are not known at this time. The risks of the procedure are related primarily to mechanical injury to the heart and vessels from catheter manipulation and the risk of thromboembolism (blood clot formation that can cause stroke). The standard risks of anesthesia also exist and include allergic reactions, medical complications and death. Risks are as follows:

- Pain or discomfort at the catheter insertion sites in the legs or neck; back discomfort from lying flat in bed during and after the procedure
- Exposure to x-ray during the procedure
- Adverse drug reactions
- Clot formation in the arteries or veins of the heart and/or lungs which can cause pain and shortness of breath
- Embolization (dislodged fragments of clots or tissue or catheter being released into the bloodstream) which could lead to stroke, heart attack or obstruction of pulmonary (lung) blood flow
- Femoral arteriovenous fistula (communication between the artery and vein)
- Pericarditis (inflammation of the lining of the heart)
- Abnormal heart rhythms, possibly requiring treatment with drugs and/or electric shock for restoration of a normal rhythm
- Infection in the bloodstream or heart tissue (which can lead to hospitalization and/or death)
- Bleeding, with the potential necessity of a blood transfusion
- Excessive or uncontrolled bleeding which can lead to stroke or death
- Collapsed lung, requiring the temporary placement of a chest tube
- Injury to major blood vessels including the coronary arteries and potentially causing a heart attack
- Perforation of the heart with bleeding into its surrounding sac, possibly requiring emergency drainage with a needle through the chest wall
- Perforation of the major vessel leaving the heart (aorta) with the subsequent creation of an abnormal opening between the atria and the aorta requiring surgical correction
- Injury to one or more heart valves
- Damage to the septal wall between the atria (upper chambers of the heart)
- Damage to the heart's normal electrical system resulting in heart block and requiring a permanent pacemaker
- Damage to or loss of a limb due to obstructed blood flow distal to the catheter insertion site
- Nerve damage
- Death

These complications are rare, and most, but not all, are treatable with little or no remaining side effects. If complications do occur, Dr. (_Name_) will treat me as appropriate. This treatment may include a surgical procedure. My participation in this study may subject me to risks which are at this time unknown. Under certain circumstances, the investigator may terminate my participation in the study without asking my permission, when it is in my best interests to do so.

If I am pregnant at the time of the procedure, the procedure will not be performed due to unforeseeable risks to the fetus or embryo.

BENEFITS

It is hoped that this procedure will prevent my atrial fibrillation from recurring or will reduce the frequency at which it occurs, or will make it easier to control with medication. I have been informed that the procedure may fail to improve my atrial fibrillation. If I have other heart rhythm problems other than atrial fibrillation, I have been made aware that this procedure is not intended to improve those other arrhythmias.

It is believed that this research may be beneficial in the future to others who have difficult to manage atrial fibrillation.

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY BENEFITS FROM THIS STUDY.

I will be told if any new information is learned which may affect my condition or influence my willingness to continue participation in this study.

While participating in this study, I should not take part in any other research project without approval from all of the investigators. This is to protect me from possible injury arising from such things as extra blood drawing, extra x-rays, interaction of research drugs, or similar hazards.

If I am pregnant at the time of the procedure, the procedure will not be performed due to unforseeable risks to the fetus or embryo.

If I am a woman who is able to become pregnant, it is expected that I will use an effective method of birth control to prevent exposing my developing baby to a potentially dangerous agent with unknown risk. If I am pregnant or currently breast feeding, I may not participate in this study. I understand that if I am pregnant, or if I become pregnant or if I am breast feeding during this study, I or my child may be exposed to a known risk of radiation (x-rays) and blood thinning agents (Coumadin, heparin).

To confirm to the extent medically possible that I am not pregnant, I agree to have a pregnancy test done within 24 hours before the procedure.

ALTERNATIVE TREATMENTS

If I do not wish to participate in this study, Dr. (__Name__) has explained that the following treatment options are available to me:

1) If I am currently taking medication, I may continue to do so and not undergo any procedure.
2) I may undergo standard catheter ablation of my heart (called AV node ablation) and the subsequent necessary implantation of a permanent pacemaker
3) I may undergo modified AV node ablation that may not require the subsequent implantation of a permanent pacemaker
4) If I am an eligible candidate, I may undergo open heart surgery (called the maze operation)

Significant new findings learned during the course of this research may affect my willingness to continue participation as a study subject. As such, I will be kept informed of significant new developments by my physician, Dr. (__Name__).

CONFIDENTIALITY

Should I choose to be a participant in this study, I will be assigned a unique study code that will not reveal my identity. This code will be used on all data and data collection forms during the study period. Any data that may be published in scientific journals will not reveal the identity of the subjects. Patient information may be provided to Federal and regulatory agencies as required. The Food and Drug Administration, for example, may inspect research records and learn my identity if this study falls within its jurisdiction. The purpose of this research is to obtain data or information on the safety and effectiveness of the REVELATION™ Tx Microcatheter System; the results will be provided to the sponsor, the Food and Drug Administration and other federal agencies as required. My medical charts and records will be made available to the study sponsor and appointed study monitors for confirmation of data collected. Every reasonable effort will be made to protect my identity and maintain my confidentiality as a study participant.

COMPENSATION

I will be compensated twenty-five dollars ($25.00) for the inconvenience and incidental expenses associated with completing Quality of Life questionnaires at each of the follow up visits that require such (Month 3 and Month 6 follow up visits) for a total of $50.00. I or my insurance company will be responsible for costs incurred related to clinical and diagnostic tests and examinations and the electrophysiology ablation procedure, admission to the hospital and any treatment of adverse events determined to be related to the procedure, as well as follow up examinations. Cardima, Inc. is providing limited financial support to the hospital and/or materials for this study.

VOLUNTARY PARTICIPATION

My decision whether or not to participate will not prejudice me or my medical care. If I decide to participate, I am free to withdraw my consent and to discontinue participation at any time without prejudice to me or effect on my medical care.

At the discretion of the principal investigator, subjects may be taken out of this study.

STUDY INFORMATION

If I have any questions, I may call _____(names and phone numbers)

All forms of medical diagnosis and treatment-whether routine or experimental-involve some risk of injury. In spite of all precautions, I might develop medical complications from participating in this study. If such complications arise, the researchers will assist me in obtaining appropriate medical treatment but this study does not provide financial assistance for additional medical or other costs. I do not waive any liability rights for personal injury by signing this form. For further information, please call _____ (number for Human Research Subjects Office): or write _____(address for Human Research Subjects Office). In addition, if I am not satisfied with the manner in which this study is being conducted or if I have any questions concerning my rights as a study participant, I may contact the Human Subjects Office at the above address and telephone number.

As a human subject, I have the following rights. These rights include, but are not limited to, the subjects' rights to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form and be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

MY SIGNATURE INDICATES THAT I HAVE READ AND UNDERSTOOD THE ABOVE INFORMATION, THAT I HAVE DISCUSSED THIS STUDY WITH THE INVESTIGATOR AND HIS STAFF, THAT I HAVE DECIDED TO PARTICIPATE BASED ON THE INFORMATION PROVIDED, AND THAT A COPY OF THIS FORM HAS BEEN GIVEN TO ME.

_____ _____
Signature Month/Day/Year

_____ _____
Witness or Investigator Signature Month/Day/Year

I have explained to the study subject the purpose of this research study and the potential benefits as well as the potential risks. The study subject has been provided a copy if this signed document.

_____ _____
Investigator Signature Month/Day/Year

C2V3

MAY 21 1999

Jack P. Douglas, Ph.D.
Regulatory Affairs Manager
Cardima, Inc.
47266 Benicia Street
P.O. Box 14172
Fremont, CA 94538

Re: IDE Number G970280/S21
Cardima REVELATION™ Tx Microcatheter System -
RA atrial fibrillation
Dated: April 22, 1999
Received: April 23, 1999

Dear Dr. Douglas:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application. Your application remains conditionally approved because your supplement adequately addressed only some of the deficiencies cited in our December 11, 1998, letter. You may continue your Phase II Limited Safety and Effectiveness Study at the institutions enrolled in your investigation where you have obtained institutional review board (IRB) approval and submitted certification of IRB approval to FDA. Your investigation is limited to 8 institutions and 30 subjects.

This approval is being granted on the condition that, within 45 days from the date of this letter, you submit information correcting the following deficiencies:

Study Endpoints

1. Please revise your safety endpoints to state the incidence of major complications to be measured during your study rather than adverse events.

2. With regard to your proposed secondary endpoint assessing Quality of Life (QOL), please describe all labeling claims you wish to make based on the QOL results. If you intend to present the QOL results in your labeling, please address the following concerns:

   a. Please provide a copy of both instruments (SF-36 and AF Severity Scale) that you have indicated to use to evaluate QOL. In addition, please describe how the SF-36 was validated for your patient population.

   b. Please state your hypotheses and perform a sample size calculation to determine whether your study will have sufficient power. Your expected change in score should be both statistically and clinically relevant. Describe your analysis plan, including what statistics will be used to evaluate multiple endpoints.

   c. Please describe your scoring methods, including methods used to combine domain sub-scales into aggregate scores.

   d. The observation period for your QOL assessment interval should correspond to your study's expected long- or short-term treatment effect. Please state and justify the assessment interval. If multiple follow-up assessments are performed, please identify which endpoint corresponds to your main quality of life hypothesis.

   e. Please state whether the questionnaire will be completed by the patient or given by an interviewer. If the patient is to complete the form independently, detailed instructions should accompany the form. If an interview method is used, the administrator should follow a script in order to minimize bias.

   f. Please describe how missing data will be tracked and managed in the statistical analysis.

Statistical Plan

3. The study hypothesis that you provided states that the rejection of the null hypothesis would require more than 50% of the patients to achieve success as defined. You have not provided, the delta required for the calculation of a sample

size. For example, if that delta is defined as 10%, more than 200 patients would be required for your study. Please define and justify a delta for your statistical assumptions.

4. The sample size calculation that you provided is not consistent with your defined study hypothesis. Your hypothesis deals with a rate of success where each patient will be classified as a success or a failure. Calculating the percent reduction of episodes across the entire patient population is not clinically relevant. Therefore, please provide revised sample size calculations consistent with the study hypothesis. The calculations should include all assumptions, formulae and parameters used (e.g., standard deviation).

5. Although you require the patients to carry a monitoring device to record episodes of AF, the data in this study are nonetheless self-reported, and thus may be subject to some degree of reporting bias. Especially worrisome would be any tendency for more zealous reporting in the screening period due to a desire to be included in the study. To help forestall this, please provide a plan to prevent patients from being made aware of the minimum of three sustained (≥30 min) episodes of AF required for full participation in the study until after the monitoring period.

6. Your protocol states that patients will be screened for three or more AF episodes prior to study entry. When including baseline measurements, the problem of " regression to the mean" could arise. This problem could potentially be exacerbated by reporting bias. For this reason, follow-up of the non-treated patients is desirable. For example, if patients who had few AF episodes in the monitoring period experienced many AF episodes in succeeding months, a warning that regression to the mean could be a distinct possibility. Therefore, please provide a plan for following patients who are enrolled in your study but are not entered into the treatment phase.

This information should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

If you do not provide this information within 45 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE application.

If you have any questions, please contact Dina Fleischer at (301) 443-8517.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular
and Respiratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

MAY - 9 2001

Ms. Marianne Baldwin
Director, Regulatory/Clinical Affairs
Cardima, Inc.
47266 Benicia Street
P.O. Box 14172
Fremont, CA 94538-7330

Re: G970280/S042
REVALATION™ Tx Microcatheter System
Dated: April 11, 2001
Received: April 13, 2001

Dear Ms. Baldwin:

The Food and Drug Administration (FDA) has reviewed the annual progress report to your investigational device exemptions (IDE) application and has determined that additional information is required. Please address the following questions and concerns:

1. The primary effectiveness endpoint of your Phase III study is an absence or reduction in the frequency of spontaneous episodes of symptomatic AF during the six months post procedure. Therefore, it will be important to ensure that patients closely follow the protocol with regard to monitoring in order to provide meaningful results. You reported that 3 of the patients were non-compliant with Holler monitoring, transtelephonic transmission and follow-up visits. Please provide a plan to decrease the number of protocol deviations, in particular the transtelephonic recordings post-procedure.

2. Per our conversation on May 3, 2001, please re-submit correct numbers for Table 16, "Reduction of arrhythmic episodes for Phase II patients."

3. It appears that the definition of acute success has changed several times in the development and implementation of the feasibility study, in the first two phases of this IDE. For example on page 18, you state that the acute success is the "a bi-directional conduction block at the isthmus line" and on page 22 you state that the acute success "no longer requires pre-pacing thresholds (because of the time required to obtain them during the procedure) in Phase II and Phase III." Please clarify how the investigators are defining sinus node dysfunction pre and post-procedure. Is there a standard definition? How does your definition effect the analysis of your safety and effectiveness data?

This information must be submitted to FDA within 45 days from the date of this letter. It should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

If you do not provide this information within 45 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE application.

If you have any questions, please contact Cindy Demian at (301) 443- 8517.

Sincerely yours,

James E. Dillard III
Director
Division of Cardiovascular
and Respiratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Memorandum

Wednesday, May 19, 1999

To: RA Files
Fr: Jack Douglas
Re: FDA Telephone Call - REVELATION Tx

A conference call was made with Dina Fleischer, FDA reviewer, myself and Vicki Hacker regarding issues involving the REVELATION Tx Phase II clinical study. Highlights from that conversation are as follows:

- Dina reiterated the phases of an AF clinical study:
  - Phase I - Safety issues are main focus (about 10 patients).
  - Phase II - Limited clinical study; safety and effectiveness (from 20-50 patients).
  - Phase III - Pivotal trial; supportive of a pre-market approval.

- Vicki reiterated the importance that Cardima maintain momentum for the study, and that abrupt start-and-stop causes problems with investigators and subject enrollment. Cardima would like to continue to place patients on monitoring cards in order to maintain momentum and screen for candidates for ablation.

- Vicki will submit a letter in about two weeks with 6 month follow-up data on 10 patients and 1 month follow-up data on a second group of 10 patients. Cardima is interested in discussing these results at a meeting scheduled for June 22.

- Will submit a supplement to monitor additional patients (up to 70), but not treat more than forty (40) patients total until reviewed by the FDA. Simply want to maintain momentum of the study for simple monitoring by heart cards.

-**Cardima's S22, currently under review, requests an additional 10 patients. Dina stated that approving the additional 10 patients probably won't be an issue now, however, the requested 20 additional pts that Jack made over the phone would need to be discussed. Dina suggested that a supplement be submitted requesting the additional patients as stated in the bullet above, and we would consider their request.** ~~Dina [illegible] the phone an additional 10 patients~~

- Dina stated that the FDA maintains the position that use of any other **manufacturer's** device (besides a Cardima catheter) at the isthmus line constitutes failure. She cautioned that the catheter would not receive an indication for treatment for atrial flutter, we would have to conduct a separate study for that indication. This may be a topic of discussion for our June meeting.

- Cardima is also interested in adding Massachusetts General Hospital as an initial investigational site as these co-investigators are instrumental to the study. **Dina suggested that Cardima submit their justification in the future supplement requesting expansion. FDA would consider their rationale at that time. However, the sponsor has been approved for an additional 8 sites, with 3 being added at a separate time. It appears that the sponsor is not in control of their investigators and the study. Vicki presented a clear justification for wanting to add Mass General, so Dina stated to submit their rationale for review.**

- Cardima is interested in modifying follow-up use of patient self-administered heart cards from each of months 1-6 to each of months 1, 3 and 6. This could be discussed in the upcoming meeting.

- Dina requested a table of data for small cohort of subjects using the Naviport **as requested in our 11/5/98 letter (S11). FDA requested that Cardima provide clinical data on the NAVIPORT catheter from a small cohort of pts prior to requesting expansion to a multi-center study.-**

- The issue of what to do with patients implanted with pacemakers needs further discussion as to the type of follow-up data needed.

- A formal progress report would be submitted to the agency once the information is obtained and prepared.

APR 7 2000

Mr. Jack Douglas
Director of Regulatory Affairs
Cardima, Inc.
47266 Benicia Street
P.O. Box 14172
Fremont, CA 94538

Re: IDE Number G970280/S35
Cardima REVELATION™ Tx Microcatheter System
Dated: March 7, 2000
Received: March 8, 2000

Dear Mr. Douglas:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application proposing the following:

1. Allow investigators to perform a second ablation procedure if necessary
2. Change patient entry criteria from excluding patients with prior CVA to excluding patients with CVA within the past 6 months
3. Allow enrollment of patients who are only refractory to amiodarone
4. Increase maximum age for enrollment from 75 to 80 years
5. Allow for study subjects who fail initial enrollment observation period(i.e., because AF frequency is too low) to reapply for study enrollment after 6 months
6. Substitute University of Chicago study center for Millburn NJ study center

For protocol change #6 (Substituting University of Chicago for Millburn NJ study center), please note that you will not be able to make this substitution because once an institution has enrolled at least one patient, that institution is considered part of the clinical study and counts toward the maximum number of allotted study centers. However, FDA is considering this submission (based on verbal confirmation by you during a telephone conversation on 4/6/00) as a request for study expansion. As a result, your IDE supplement proposing an expansion of your investigation to include one additional institution and your request for protocol changes (items 2-5) is approved. You may implement these changes at the institutions enrolled in your investigation after you have obtained institutional review board (IRB) approval and submitted certification of IRB approval to FDA. Your investigation is limited to 10 institutions and 20 subjects.

However, your request for item 1 is conditionally approved, and you may also implement this change at the institutions enrolled in your investigation. This approval is being granted on the condition that, within 45 days from the date of this letter, you submit information correcting the following deficiency:

For protocol change #1 (Allowing investigators to perform a second ablation procedure), please submit a modified investigational plan using a Blanking Period according to the following proposed guidelines:

FDA recognizes that some of the patients treated in your study may require an additional ablation procedure to terminate an arrhythmia(s) (e.g., a typical atrial flutter) that may be masked by the original atrial fibrillation or that may develop after the initial procedure with changes in the cardiac substrate. As a result, investigators may treat non-AF arrhythmias or AF recurrences during the initial ablation procedure or at a subsequent treatment session.

FDA recommends that you incorporate into your study design a pre-defined blanking period (not to exceed 4 months) to allow for subsequent ablation procedures. Special consideration should be given to the following issues relating to the blanking period:

a) The blanking period will provide for the potential delay in recovery of the treated cardiac chambers.

b) During the blanking period, supplemental procedures for the ablation treatment may be performed with investigational devices at the discretion of the investigator.

c) Procedural and clinical event data should be collected, tabulated, and analyzed for the supplemental procedures performed during the blanking period.

d) Because your study is intended to support the marketing claims for a defined ablation treatment system, only the investigational system should be used during the blanking period. If a patient requires an additional treatment with a non-investigational device during the blanking period, the patient should be considered an acute failure.

e) The defined (6 month) follow-up period should begin at the conclusion of the blanking period.

f) After the blanking period, episodes of sustained AF will be categorized as a recurrence of arrhythmia.

This information should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

If you do not provide this information within 45 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE application.

We would like to point out that FDA approval of your IDE supplement does not imply that this investigation will develop sufficient safety and effectiveness data to assure FDA approval of a premarket approval (PMA) application for this device. You may obtain the guideline for the preparation of a PMA application, entitled "Premarket Approval (PMA) Manual," from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597.

You should also give serious consideration to the following item which is considered important for the analysis of your data for the purposes of determining safety and effectiveness for a future PMA application:

Please be advised that if too many study centers have treated only one or several patients, you may have difficulty in demonstrating poolability of your safety and effectiveness results from your clinical study.

If you have any questions, please contact Stuart Portnoy, MD at (301) 443-8525 x 180.

Sincerely yours,

WB for

James E. Dillard III
Director
Division of Cardiovascular and Respiratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

CARDIMA™

MEMORANDUM

DATE: Thursday, April 20, 2000

TO: REVELATION™ Tx Project File

FROM: Jack Douglas

SUBJECT: REVELATION™ Tx IDE MEETING

FDA Attendees: Megan Moynahan, Stuart Portnoy. MD; Gary Kamer, Nancy Brogden, Dina Fleischer (by phone).
Cardima Attendees: Jack Douglas, PhD, Allan Abati, PhD, Roger Marinchak, MD, Phil Radlick, PhD. Kushal Vepa, Harrison Stubbs, PhD.

Note: Specific discussion is noted by bullet points.

A meeting was held Thursday, April 13, 2000 to discuss the REVELATION™ Tx IDE (G970280) project with the Office of Device Evaluation (ODE) in Gaithersburg, MD. The agenda for the meeting was:

1. Outline of Agreement bullet points.
2. Description of device and system.
3. Review of Phase I / II Results.
4. Review of Phase III statistical plan, NavAblator catheter and DSMB.
5. Overall discussion.

- J. Douglas presented bullet points that Cardima would like to have agreement with the FDA.
    - It was noted by M. Moyhahan and N. Brogden that it would not be appropriate to request an Agreement Meeting at this time as there were supplements pending review.
- J. Douglas also reviewed overall Phase II Objectives, Selection criteria, Set-up, Procedure, Follow-up plan, and recent study changes submitted in a supplement.
    - Cardima presented a plan by which a subject can receive a second procedure within 6 months after the intial treatment. The six month follow-up periods for such subjects will be from the time of the second procedure.
    - The FDA requested a "blanking period" be instituted for 1-3 months following intial treatment to provide for healing response.
    - A response letter to the supplement was issued and would need to be reviewed by the company.
- A. Abati presented clinical results of Phase I and II studies. Also presented some data from Europe that corroborated the US results.
    - The FDA noted to Cardima that in future progress reports adverse events should be noted as minor or major according to definitions provided by the FDA, and as specified in the original IDE.

CONFIDENTIAL

- In looking at the results from Phase I and II, M. Moynahan noted that she didn't realize that the determination of the follow-up effectiveness endpoint of number of episodes relative to baseline was for the "sixth month" as opposed to for 'six months". Cardima noted this was what was agreed to in the original IDE and noted in supplements.

- H. Stubbs discussed two statistical issues relative to the Phase III study.

  - "Sliding Scale" for defining subject success was discussed per last year's recommendation by the FDA and provided by H Stubbs. A request from Dr. Marinchak was made to adjust the percentage reductions required for subject success to be at least 50%. For 3-4 episodes/month, the minimum should remain at 75%.
  - Table 12 "Confidence Limits" in the IDE package was discussed and noted to provide acceptable statistical precision for the Phase III study results.
  - The sample size of enrolled patients for Phase III would need to be adjusted for patient ineligibility due to insufficient number of baseline episodes.

- K. Vepa presented a description of the NavAblator and animal study results.

- J. Douglas presented ideas for employing a DSMB into the study.

  - The FDA reiterated that a DSMB is a good idea, but specific rules were not discussed. Need to describe purpose, details of procedure, meetings, minutes, etc. DSMB should focus on safety, but still need a statistician to put safety data in perspective.

- FDA Follow-up Discussion and Action Items.
  - Need to still count all subjects that sign consent as enrolled. Company needs to account for those that do not enroll. If necessary, request for more subjects in order to meet treatment and follow-up objective.
  - Still counting all subjects treated with off-label catheters as acute treatment failures.
  - The QOL information is still being reviewed by the agency.
  - Regarding the NavAblator, and pending more detailed review of the test and study data, the FDA agreed that the catheter could be used in the study. A supplement would need to be submitted.
  - No blanking period will be needed due to the structure of the study and the reporting of effectveness results at the sixth month.
  - Cardima would like the study to stand on its own merits based on Phase III data. It will be supported by Phase I and II data, and the European experience, secondarily.
  - Need to change sample size discussion in the IDE, along with other items from past supplements and submit a revised study protocol.
  - Will outline a procedure for DSMB meetings.

CONFIDENTIAL

Moynahan, Megan

From: Moynahan, Megan
Sent: Friday, June 23, 2000 4:47 PM
To: 'Jack Douglas'
Cc: Portnoy, Stuart; Provost, Miriam; Fleischer, Dina J.; Kamer, Gary L.
Subject: RE: G970280/S38

In our meeting on April 13, 2000, we raised a couple points regarding your pivotal (Phase III) study protocol. They included:

- that the use of off-protocol catheters would render a patient a study failure;
- that you should use the sliding-scale to categorize patients as successes or failures; and
- that the definition of an enrolled patient includes anyone who signs the Informed Consent.

In my review of your supplement, I noted that you successfully implemented those changes in your Phase III study protocol. HOWEVER, we also asked that you to apply those new "rules" to your existing data set (Phases I and II), in order to begin to predict the success rate of your device, and to see the confidence intervals around that number.

Therefore, I'd like to clarify the deficiency in the letter dated 6/8/00:

- Please provide an estimate (and 95% confidence bounds) for your device's effectiveness by applying the success definitions of your Phase III protocol to the data acquired in Phases I and II (combined). In addition, please specify the method (e.g., equations) that will be used to calculate the upper and lower confidence bounds.

I hope this has clarified my request. If you still feel like we need a conference call, let me know.

Megan

-----Original Message-----
From: Jack Douglas [SMTP:jack.douglas@cardima.com]
Sent: Tuesday, June 20, 2000 6:40 PM
To: Megan Moynahan
Subject: re: G970280/S38

Hi Megan

We are unclear regarding a question in the June 8 conditional approval letter for the above study that concerns a study hypothesis. Based on earlier meetings with the FDA, we changed to a method using confidence intervals, and have eliminated a study hypothesis.

Perhaps we can discuss this with Gary Kramer before we send in a response? Could you suggest a time we could call after 10am PDT?

Thanks,

Jack Douglas

CARDIMA®

Tuesday, July 18, 2000

Document Mail Center (HFZ-401)
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
9200 Corporate Blvd.
Rockville, MD 20850

Attn: Megan Moynahan

Re: **REVELATION™ Tx Microcatheter and NavAblator™ System** (G970280)
FDA Request for Additional Information; Request for Additional Sites; Procedural Change

Dear Ms. Moynahan,

We are writing in response to an FDA letter dated June 8, 2000, and e-mail correspondence dated June 23, 2000, requesting additional information regarding the primary study effectiveness endpoint using current Phase I and Phase II data.

Per a June 23 e-mail, we understand that the FDA is interested in an estimate of Phase III effectiveness (with 95% CI) using the Phase III protocol definition of success (modified "sliding scale"), and the following criteria:

- That the use of off-protocol catheters would render a subject a study failure;
- That you should use the sliding scale to categorize subjects as successes or failures; and
- That the definition of an enrolled patient includes anyone who signs the Informed Consent.

In both Phases I and II, however, most subjects were treated "off-label" with other products at the cardiac isthmus, and an estimate of effectiveness is therefore not possible. Excluding the first criterion for the moment, an estimate of success with exact CI for success using the binomial distribution can be provided. Using the most current Phase I and Phase II sixth month follow-up data, each subject was determined as either a success or failure (see accompanying table). Using these data, an overall rate of success and 95% CI would be 63.6% with upper and lower confidence limits of 45.1% and 79.6%, respectively. The success rate and CI for the Phase II subjects alone is 72.0% with 95% lower and upper confidence limits of 50.6% and 87.9%, respectively.

In addition, Cardima would like to request permission to expand to a total of twenty (20) sites. Some sites which have enrolled very few subjects in Phase I or Phase II are most likely not going to contribute more subjects, and may be asked to discontinue participation in the study.

Finally, Cardima is also providing notice of a procedural change to totally eliminate the use of Holter monitoring. Their use to obtain a single day of data has limited value in the context of this study versus the inconvenience and cost of their use. Primary endpoint AF episode data will be continued to be evaluated using standard self-administered, heart card monitoring devices.

56-9

78

47266 Benicia Street P.O. Box 14172 Fremont, CA 94538-7330 Phone 510.354.0300 Fax 510.657.4476 http://www.cardima.com

CARDIMA™

Revelation TX Microcatheter System

Protocol No. C-98-100-AF
RF ABLATION DATA • PAGE ____ of ____
Form ABF WORKSHEET

Subject Initials ☐ FI ☐ MI ☐ LI Subject ID Number ☐☐☐☐

Pathfinder™AFTC

Lot No.	Serial No.
☐☐☐☐☐	☐☐☐☐ TC
☐☐☐☐☐	☐☐☐☐ TC

Location: ☐ A) SVC to IVC ☐ B) IVC to (septal) ☐ C) IVC to TA ☐ D) Other: _____

Guiding catheter:

Manufacturer: _____ **Size:** ☐ 6 Fr ☐ 7 Fr ☐ 8 Fr **Shape:** ☐ IMA ☐ LCB ☐ MB ☐ Hockey ☐ Josephson ☐ Demato ☐ Other _____

_____ ☐ 6 Fr ☐ 7 Fr ☐ 8 Fr ☐ IMA ☐ LCB ☐ MB ☐ Hockey ☐ Josephson ☐ Demato ☐ Other _____

ABLATION DATA

TIME	ELECTRODE(S)	BIPOLAR THRES. PRE (mA)		EKG AMPLITUDE PRE (mV)	IMPEDANCE (ohms) Rise > 10 ohms	TEMP °C	POWER	DURATION (secs)	BIPOLAR THRES. POST (mA)		EKG AMPLITUDE POST (mV)	COMMENTS
		Electrode Pair	Pacing Thres.						Electrode Pair	Pacing Thres.		
					☐ Yes ☐ No							
					☐ Yes ☐ No							
					☐ Yes ☐ No							
					☐ Yes ☐ No							
					☐ Yes ☐ No							
					☐ Yes ☐ No							
					☐ Yes ☐ No							
					☐ Yes ☐ No							
					☐ Yes ☐ No							
					☐ Yes ☐ No							
					☐ Yes ☐ No							
					☐ Yes ☐ No							
					☐ Yes ☐ No							
					☐ Yes ☐ No							
					☐ Yes ☐ No							

1. Was Revelation TX removed for inspection: ☐ Yes ☐ No Serial No. _____
   If Yes, describe: Appearance ☐ Unchanged ☐ Damaged (describe) _____ Thrombus Formation ☐ Yes ☐ No _____ Describe location and size
2. Was any catheter other than the Revelation TX used for RF energy delivery? ☐ Yes ☐ No
   If Yes, time inserted: ☐☐ : ☐☐ Time removed: ☐☐ : ☐☐ Manufacturer: _____ Model: _____

• COMPLETE ALL ITEMS. ITEMS MISSING OR INCONSISTENT WILL REQUIRE ADDITIONAL FOLLOW-UP •

000284

CARDIMA™

Revelation TX Microcatheter System

Protocol No. C-98-100-AF
RF ABLATION DATA • PAGE ____ of ____
Form ABF SUMMARY

Subject Initials ☐ FI ☐ MI ☐ LI Subject ID Number ☐☐☐☐

Pathfinder™AFTC

Lot No.	Serial No.
☐☐☐☐☐	☐☐☐☐ TC
☐☐☐☐☐	☐☐☐☐ TC

Location: ☐ A) SVC to IVC ☐ B) IVC to (septal) ☐ C) IVC to TA ☐ D) Other: _____

Guiding catheter:

Manufacturer:	Size:	Shape:
_____	☐ 6 Fr ☐ 7 Fr ☐ 8 Fr	☐ IMA ☐ LCB ☐ MB ☐ Hockey ☐ Josephson ☐ Demato ☐ Other _____
_____	☐ 6 Fr ☐ 7 Fr ☐ 8 Fr	☐ IMA ☐ LCB ☐ MB ☐ Hockey ☐ Josephson ☐ Demato ☐ Other _____

ABLATION DATA

POSITION	ELECTRODE(S)	BIPOLAR THRES. PRE (mA)	EKG AMPLITUDE PRE (mV)	IMPEDANCE (ohms) Rise > 10 ohms	BIPOLAR THRES. POST (mA)	EKG AMPLITUDE POST (mV)	COMMENTS
	1 - 2			☐ Yes ☐ No			
	3 - 4			☐ Yes ☐ No			
	5 - 6			☐ Yes ☐ No			
	7 - 8			☐ Yes ☐ No			
	1 - 2			☐ Yes ☐ No			
	3 - 4			☐ Yes ☐ No			
	5 - 6			☐ Yes ☐ No			
	7 - 8			☐ Yes ☐ No			
	1 - 2			☐ Yes ☐ No			
	3 - 4			☐ Yes ☐ No			
	5 - 6			☐ Yes ☐ No			
	7 - 8			☐ Yes ☐ No			

1. Was Revelation TX removed for inspection: ☐ Yes ☐ No Serial No. _____
   If Yes, describe: Appearance ☐ Unchanged ☐ Damaged (describe) _____ Thrombus Formation ☐ Yes ☐ No _____ Describe location and size
2. Was any catheter other than the Revelation TX used for RF energy delivery? ☐ Yes ☐ No
   If Yes, time inserted: ☐☐ : ☐☐ Time removed: ☐☐ : ☐☐ Manufacturer: _____ Model: _____

• COMPLETE ALL ITEMS. ITEMS MISSING OR INCONSISTENT WILL REQUIRE ADDITIONAL FOLLOW-UP •

Table 4
Procedural Pacing Threshold and Electrogram Amplitude
Pre- and Post-Ablation Phases I and II
n=20

	Pacing Threshold* (mA)				Electrogram Amplitude* (mV)			
Subject #	Number of paired values	mean pre	mean post	% change	Number of paired values	mean pre	mean post	% change
Phase I								
	4	2.75	5.50	100	4	1.61	1.22	-24
	11	2.90	5.87	102	11	1.63	1.02	-37
	23	3.41	7.28	113	23	1.46	0.87	-40
	22	8.27	17.27	109	23	0.93	0.69	-26
	22	13.91	25.48	83	37	1.35	1.00	-26
	34	9.20	17.32	88	34	0.59	0.36	-39
	21	3.58	7.70	115	24	0.99	0.67	-32
	14	3.82	8.38	119	21	1.04	0.38	-63
	32	5.84	9.77	67	31	1.61	0.75	-53
	22	7.75	9.97	29	22	1.35	0.53	-61
Mean ± SE		6.14 ± 1.15	11.4 ± 2.05†	92.5 ± 8.72		1.26 ± 0.11	0.75 ± 0.09†	-40.1 ± 4.55
Phase II								
	24	5.3	13.6	157	24	0.97	0.50	-48%
	11	3.7	8.2	124	11	0.85	0.31	-64%
	7	3.8	6.7	77	7	0.55	0.31	-44%
	13	4.7	7.4	57	13	0.34	0.20	-40%
	11	5.0	8.9	79	11	1.16	0.96	-17%
	13	5.5	18.4	237	13	1.19	0.34	-71%
	12	3.1	8.0	157	12	0.54	0.19	-65%
	13	4.4	9.2	109	13	0.85	0.45	-46%
	15	5.0	10.8	115	15	1.14	0.37	-68%
	11	2.7	7.1	166	11	1.79	0.68	-62%
Mean ± SE		4.3 ± 0.3	9.8 ± 1.2†	128 ± 18		0.94 ± 0.14	0.43 ± 0.08†	-53 ± 6
Totals for Phases I and II								
Mean ± SE		5.2 ± 0.6	10.7 ± 1.2†	113 ± 11		1.1 ± 0.1	0.6 ± 0.1†	-46 ± 4

* Mean of all electrode pairs for which pre- and post-ablation values were both available.
^ Subject [redacted] Paired pacing thresholds and electrogram amplitudes are available for the septal line only.
† Paired T-test (post- vs. pre-ablation), $p < 0.001$.

82

G970280 SG34
C2 V4
SG-7

ARDIMA®

Thursday, March 02, 2000

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850
Attention: Jennifer L. Goode, ODE/DCRND/Pacing and EP Devices Group

Re: REVELATION™ Tx Microcatheter System (G970280)
NavAblator Catheter

Dear Jennifer:

We are planning to submit an IDE supplement for a new catheter currently referred to as the NavAblator. The NavAblator will be used in conjunction with the REVELATION Tx Microcatheter System used for treatment of atrial fibrillation as outlined in the above IDE.

In this forthcoming IDE supplement, Cardima would like to preclude submission of additional biocompatibility data since the device is fabricated with blood-contacting materials equivalent to those found in other Cardima devices previously reviewed by the FDA. Specifically, the NavAblator is a hybrid, composed of materials originally used in the Cardima PATHFINDER™, NAVIPORT™, and REVELATION™ Tx catheters.

Figure 1 shows a schematic of the device, including a cross section with materials identified. The distal section of the NavAblator is composed of a polyurethane shaft and distal platinum/iridium (Pt/Ir) electrodes, using material identical to other marketed Cardima products. The NavAblator is designed to deflect, which is accomplished using an internal wire attached at the tip (see cross section). A small amount of Au/Sn solder is used to affix the wire at the tip via a 0.025" window, also noted in the schematic.

Figure 2 shows a photo of the distal section of the device, showing the polyurethane shaft, distal Pt/Ir ablation electrode and three accompanying Pt/Ir mapping electrodes.

Table 1 on the following page lists the materials used to construct the NavAblator. Each material is listed, along with the component, material grade, chemical composition, vendor, and a reference to the relevant predicate device. As noted in the table, all blood-contacting materials are identical to those found in other Cardima products. Biocompatibility test data have been previously submitted and accepted. There is also a large amount of field experience with the marketed devices, which has not included reports of biocompatibility complications. Two non blood-contacting materials, a cyanoacrylate glue and a tin solder, have been introduced which are very similar to products used previously. Since these products do not make blood contact, and are very similar to previous products, further testing is not warranted.

Finally, in order to support a claim that additional biocompatibility testing is not needed, a Biocompatibility Certification is also included per FDA request. For further information, I can be contacted at (510) 354-0166 or at jack.douglas@cardima.com.

Sincerely,

Jack F. Douglas, Ph.D.
Director of Regulatory Affairs

called 3/8/00 and concurred with their rationale for omission of additional biocompatibility testing. No Response Necessary
Jennifer L. Goode 3/9/00
Concur CMMagnel

275

47266 Benicia Street P.O. Box 14172 Fremont, CA 94538-7330 Phone 510.354.0300 Fax 510.657.4476 http://www.cardima.com

December 17, 2002

Elias Mallis, Chief
Electrophysiology and Monitoring Devices Branch
Food and Drug Administration
Center for Devices and Radiological Health
IDE Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, MD 20850

Re: IDE #G970280/S56 – REVELATION™ Tx Microcatheter System – *Expanded Enrollment*

Dear Mr. Mallis:

Cardima would like to amend the request submitted in supplement #S55 with a letter dated December 6, 2002 for approval to expand the above-referenced investigation to additional patients. Following our telephone conversation of December 13, 2002, Cardima is requesting expanded enrollment in the referenced IDE study to permit enrollment of up to 230 patients and treatment and follow up of 130 (an increase of 50) study subjects.

In addition, Cardima has amended the study protocol to require the use of only investigational ablation catheters, including at the isthmus line. A full copy of the revised protocol is enclosed with this letter.

If there are any questions regarding this supplement please contact me directly at 510-354-0166 or by email at marianne.baldwin@cardima.com.

Cardima, Inc. considers the information described in this letter to be confidential commercial information, and therefore exempt from public disclosure. Consequently, we request that this supplement be treated as confidential in accordance with 21 CFR 20.61b.

Best regards,

Marianne Baldwin
Vice President,
Regulatory, Clinical, Quality
Cardima, Inc.

3.10. Study Procedure

3.10.1. Patient Preparation

1) If subject on Coumadin, discontinue three (3) days prior to the procedure. Heparin or low molecular weight heparin may be administered one (1) day prior to the procedure at the discretion of the investigator. At the time of the procedure the INR should be <1.8.
2) Once the subject has been brought to the electrophysiology laboratory, attach the RF generator ground patch securely to the subject's skin with a sufficient quantity of conductive gel. Attach electrocardiogram monitoring equipment to the patient using standard hospital procedure and prepare the patient in the usual fashion using sterile technique.
3) Place an introducer sheath that will accommodate the outer diameter of the Cardima™ Naviport 8F guide in the Femoral and/or Jugular Vein.
4) Place other introducer sheaths as deemed necessary by the investigator.
5) Obtain a baseline activated clotting time (ACT) value. Administer a bolus of intravenous heparin and infuse heparin continuously throughout the procedure to maintain an ACT of approximately 200 to 300 seconds. Take ACT measurements at 30 minute intervals until therapeutic levels are achieved. Thereafter, maintain therapeutic levels per standard hospital procedure. Adjust heparin according to the ACT values.
6) Place standard diagnostic EP catheters as necessary.

3.10.2. Pre-Procedure Diagnostic Assessment

Perform standard mapping procedures according to routine practice. Record Atrial-His intervals.

3.10.3. Ablation Procedure

The lesions shall be formed using the REVELATION Tx (with the Naviport deflectable guiding sheath) for the lateral and septal lines and for the formation of an isthmus line.

If achievement of bi-directional block at the isthmus with the Tx/Naviport combination is not possible due to the isthmus anatomy, use the NavAblator to complete the isthmus line. The NavAblator alone or the NavAblator with a commercially available flutter sheath may be used to complete this lesion.

3.10.4. REVELATION™ Tx System Setup (see Figure 1)

1) Connect the Cardima™ Switchbox to the Cardima™ Connecting Cable and the RF generator per the Switchbox Instructions For Use.
2) Connect the guiding catheter.

Note: The Naviport Deflectable Tip Guiding Catheter will be made available to the physicians as part of this investigation. The Cardima™ Naviport guiding catheter is available in 10 mm, 30 mm, 40 mm, 50 mm and 60 mm curve reach and is recommended for placing the REVELATION™ Tx in all trajectories. The Cardima™ Naviport guiding catheter with a 10 mm curve reach is recommended for the isthmus trajectory. If the

126

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service Food and Drug Administration

MEMORANDUM

DATE: **December 5, 2001**

FROM: Cindy Demian, Biomedical Engineer

TO: G970280/S047
RE: Cardima, Inc.
Revelation™ Tx Microcatheter System

CONTACT: Marianne Baldwin, Vice President, Regulatory, Clinical, Quality (510) 354-0166

HISTORY

The Revelation™ Tx catheter is a temperature sensing radiofrequency ablation microcatheter with multiple 6mm electrodes providing an overall working electrode length of 62mm.

Intended use: cardiac electrophysiology procedures to map, pace and ablate cardiac tissue within the right atrium in those patients who have symptomatic paroxysmal atrial fibrillation.

REASON FOR SUBMISSION

The sponsor submitted an updated investigators list. In addition, this supplement included protocol changes. Dr. Lesley Ewing provided a clinical consult (see attached memo) and her concerns are below:

1. The sponsor wants to change femoral arteriovenous fistula to a minor adverse event, even if hospitalization is required to repair the fistula (page 27 of the new protocol). **Dr. Ewing strongly disagrees with this. The definition that we currently use for adverse events (from the regulation describing adverse events) would define this also as an adverse event. To be consistent between the various IDE studies an AV fistula should be considered an adverse event.**

2. The sponsor wants to change the definition of clinical success from "reduction of frequency of symptomatic episodes of paroxysmal atrial fibrillation as compare to the frequency of symptomatic episodes pre-procedure" to the same statement "with or without medication therapy (on page 28 of the updated protocol)." **In previous ablation procedures we have regarded the patient who required medication after the procedure for treatment of symptoms caused by the targeted dysrhythmia as ablation failure.**

On December 5, 2001, I called the sponsor (along with Dr. Ewing, Medical Officer, and Elias Mallis, Acting Branch Chief for CEMB) to discuss the above concerns. The following action items were agreed upon:

1. The sponsor should revise their protocol to reflect AV fistula as a major adverse event (on page 27) as stated in the regulation. The sponsor satisfies this deficiency by indicating the following (on page 28 of their protocol):

"In the event that a patient requires significant intervention (e.g., blood transfusion, surgery) in response to an adverse event it will be considered a major complication."

2. The sponsor should remove "with or without medication therapy (on page 28)"from their protocol.

The concern with item #2 was that if there is a change in dosage (either an increase or decrease), this is considered to be a "new" medication. Then the question should be raised, "How do you determine if the device is a success or if it's the medication?" The sponsor would have a dilemma trying to separate the data, which could not be pooled. Therefore, it was agreed that the sponsor remain with the original primary endpoint definition (on page 11), see below:

1) To evaluate whether subjects with drug refactory symptomatic paroxysmal AF treated with RF ablation using the REVELATION™ Tx, and optionally the NavABlator™, report an absence or reduction in the frequency of spontaneous episodes of symptomatic AF during the sixth month post procedure, while either maintained on the same anti-arrhythmic drug regimen or a reduced dosage.

The sponsor submitted these revisions by fax (dated December 5, 2001) and will follow up with a hard copy. In addition, the sponsor informed the FDA that they currently have enrolled 37 patients and plan to complete their study sometime in 2002.

RECOMMENDATION- Approval to Change in Protocol (AP)

Cindy Demian

Cindy Demian, MS., Lead Reviewer
Cardiac Electrophysiology & Monitoring Branch

Dec. 12, 2001
Date

Concur

Elias Mallis, (Acting) Branch Chief
Cardiac Electrophysiology & Monitoring Branch

Date

CARDIMA®

December 5, 2001

Elias Mallis, Acting Branch Chief
IDE Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Cardiac Electrophysiology & Monitoring Devices Branch
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850

Re: IDE #G970280/S46 – Request for More Information
REVELATION™ Tx Microcatheter System

Dear Ms. Mallis:

Pursuant to our telephone conversation today regarding the IDE Supplement identified here as S46 (but referenced as S47 in our phone conversation), Cardima is submitting additional information to clarify the protocol modifications identified in that supplement.

Cardima's proposed modification to identify an AV fistula that required hospitalization as a "minor complication" has been changed to reflect this complication as a "major complication" if it requires hospitalization. It is understood that this classification of this particular complication permits a standardized referral point when considering complications for EP catheterization procedures. This change has been made to page 27 of the revised protocol, a copy of which is included with this letter. The list of major and minor complications has been changed to reflect the previously approved list of major and minor complications.

Additionally, Cardima wishes to clarify that the stated clinical success criteria for measurement was intended to reflect the "Primary Objectives" as stated on page 11 of the protocol. In that regard, page 28 of the protocol has been to reflect the originally approved language on page 11 "...while either maintained on the same anti-arrhythmic drug regimen or a reduced dosage." A copy of that page is included with this letter, as well.

47266 Benicia Street P.O. Box 14172 Fremont, CA 94538-7330 Phone 510.354.0300 Fax 510.657.4476 http://www.cardima.com

Cardima will advise all clinical sites of these changes and will forward a copy of the full protocol with the changes referenced herein to the Agency and to our clinical sites as well.

If you have any questions or comments concerning this report, please do not hesitate to call me at (888) 354-0300 or direct at (510) 354-0166.

Sincerely,

Cardima, Inc.
Marianne Baldwin
Vice President, Regulatory, Clinical, Quality

If the subject remains on Coumadin at subsequent follow up visits, the investigator will obtain PT and INR values per institutional protocol.

In addition to the follow-up visits, the subject will be contacted by telephone 24 months following the ablation procedure to establish changes in the patient's status (i.e., number of episodes of AF, number of visits to the emergency room, number of days of hospitalization, changes in medications, etc.) and to determine the incidence of any adverse events.

3.11.4. Adverse Effects

Any and all complications/adverse effects that occur during the course of this study will be recorded. Data to be collected will include the nature of the complication or adverse effect, onset and resolution dates and time (or whether the complication is ongoing), severity, management, outcome, and documentation of device involvement. Complications will be tabulated as "major" or "minor" per the FDA definition (see Section 5). From these data rates of major and minor complications will be determined. In addition, the number of anticipated and unanticipated adverse effects that occur in the study population will be tabulated and summarized. The incidence of all types of complications and adverse effects will be reviewed during the course of the study for any indications that use of the investigational device confers any unanticipated significant risk.

3.11.5. Anticipated Adverse Effects

Possible adverse effects that may be anticipated in association with the investigational devices and procedure are listed below by likely category of complication:

Major Adverse Effects (may be considered either device or procedure-related):

- Death
- Myocardial infarction
- Stroke
- Valve or cardiac structure damage
- Atrio-ventricular block possibly requiring a permanent pacemaker
- Sino-atrial block possibly requiring a permanent pacemaker
- Thromboembolism
- Pulmonary embolus
- Endocarditis
- Cardiac perforation and/or resulting hemopericardium and/or tamponade
- Nerve damage
- Pneumothorax
- Arrhythmias, possibly requiring drugs and/or DC cardioversion
- Phrenic nerve injury

Minor Adverse Effects (may be considered either device or procedure-related):

- Infection
- Bleeding
- Femoral arteriovenous fistula
- Femoral artery injury
- Pericardial effusion

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

- Drug reactions

In the event that a patient requires significant intervention (e.g., blood transfusion, surgery) in response to an adverse effect it will be considered a major complication.

3.11.6. Criteria for Measuring Effectiveness

3.11.6.1. Method of Evaluation

The assessment of the effectiveness of the REVELATION™ Tx and the NavAblator™ in the treatment of AF will be based on the following endpoints:

The procedural endpoint of this study is:

Electrogram amplitudes post-ablation relative to pre-ablation

The primary clinical endpoints are:

1) Frequency of any spontaneous symptomatic episodes of AF experienced by subjects
2) Incidence of adverse effects

The secondary clinical endpoint is:

Quality of life based on the SF-36 and symptoms and severity based on the AFSS

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

Clinical (Patient) Success:

The clinical effectiveness of ablation with the REVELATION™ Tx will be established based on achieving the following outcome by the sixth-month of follow-up:

1) Reduction of frequency of symptomatic episodes of paroxysmal AF as compared to the frequency of symptomatic episodes pre-procedure with or while either maintained on the same anti-arrhythmic drug regimen or a reduced dosage.

2) Improvement in the quality of life as measured by the SF-36 and the AFSS

Cardima Revelation Tx Microcatheter System and NavAblator Ablation Catheter

P020039

William H. Maisel, MD, MPH

Chair, FDA Circulatory System Medical Devices Panel

Director, Arrhythmia Clinical Research

Brigham and Women's Hospital

Boston, MA

Overview of Comments

- Panel Meeting Issues - May 2003
- Amendment 6 responses – January 2004
- A little perspective on the importance of AFIB
- Conclusions

Minimal Additional Data in Amendment 6

Phase IIa – Feasibility 10 pts
Phase IIb – Expanded Feasibility 38 pts
Phase III – Pivotal 82 pts

Phase IIb and III submitted to support marketing application to Panel.

P020039/A006

- Focuses on Phase 3 trial
- States that "An additional 36 pts are included". That should be 82 + 36 = 118 but the total number of pts is 98. In reality, data from an additional 16 patients has been submitted.

Circulatory System Device Advisory Panel Meeting – May 2003

- Lack of An Accurate Measurement of the Primary Effectiveness Endpoints

- Lack of a Consistently Defined Procedural Endpoint

Lack of Accurate Measurement of Effectiveness Endpoint

- Primary Endpoint defined as:

  "reduction in frequency of symptomatic episodes of AFIB during the 6th month of follow-up compared to baseline frequency"

- During the 6th month post-procedure time period, patients were supposed to transmit a recording:

  1) When they were symptomatic

  2) Weekly whether or not they were symptomatic

Lack of Accurate Measurement of Effectiveness Endpoint

- In panel submission - close to 2/3 of patients did not make the minimum number of transmissions

- In Amendment 6, the sponsor notes that 77.4% of patients provided 4 or more transmissions and 88.7% provided 3 or more transmissions during the 6th month of follow-up.

BUT

- **The number of patients that were compliant with the actual protocol is not stated.**
- **It appears that the majority WERE NOT compliant with the required transmissions.**
- **This makes the datas interpretation with regard to EFFECTIVENESS impossible.**

Cardima P020039

Lack of consistently defined procedural endpoint

Procedural success was defined in the protocol as demonstration of at least one of the following:

- reduction in the amplitude
- fragmentation or widening of the local electrogram
- appearance as split potentials
- an increase in the pacing threshold.

- These procedural endpoints were not consistently measured or recorded on the data forms

- Endpoints poorly defined with regard to RF duration, temperature goals, amplitude reduction specifics

- Endpoints were poorly measured during clinical trial

Lack of consistently defined procedural endpoint

AMENDMENT 6 - Page 82/293

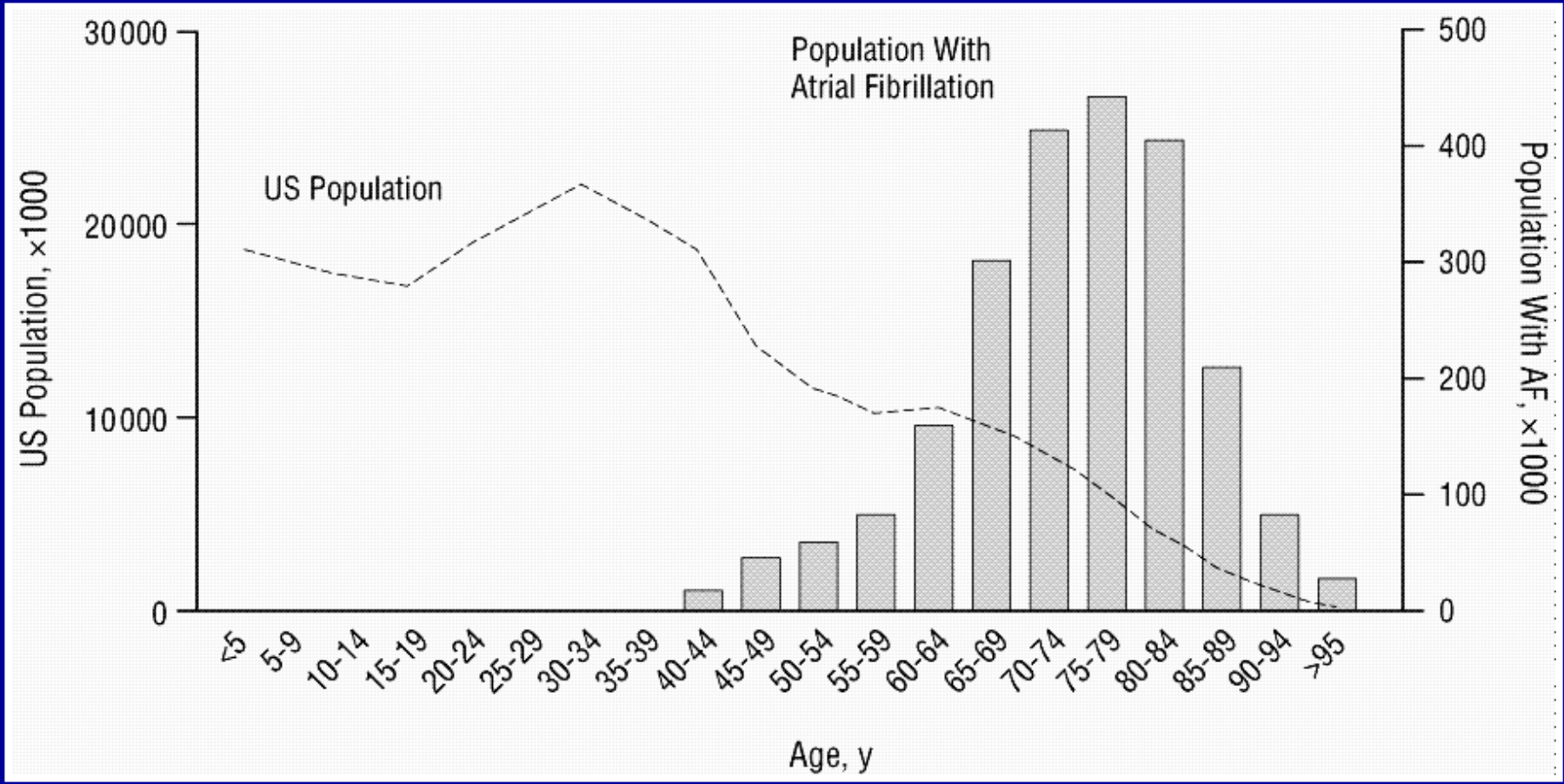
- There should be 196 data points per RF electrode (98 patients x 2 lines - posterolateral and septal). The data presented shows 41-58 data points per electrode (i.e. over 2/3 of the data is missing).

- 78% of procedures had pre and post ablation paired electrode egm amplitude measurements. Therefore in 22% of the procedures, no acute amplitude change endpoints were measured AT ALL.

As discussed extensively at the Panel meeting, this clinical study had poorly defined endpoints that were not consistently measured.

The lack of a consistently defined endpoint remains a SIGNFICIANT ISSUE that is not adequately addressed by the resubmission

Epidemiology of Atrial Fibrillation



Over 2 million Americans Have Atrial Fibrillation

Feinberg WM, Arch Int Med 1995

Cardima P020039

Conclusions

Cardima Revelation Tx Microcatheter System and NavAblator Ablation Catheter

P020039

1. The device remains NOT APPROVABLE because of a lack of adequate data supporting EFFECTIVENESS and SAFETY
2. The data already submitted could still be used to support the SAFETY of the device
3. Additional data is needed re: EFFECTIVENESS

MEMORANDUM

March 9, 2005

To: Ms. Lisa Leveille
DCD/ODE/CDRH/FDA

From: William H. Maisel, MD, MPH
Chair, Circulatory System Medical Devices Panel

Re: P020039
Cardima Revelation Tx Microcatheter System and NavAblator Ablation Catheter

---

Attached please find my comments regarding the above referenced submission.

P020039
Cardima Revelation Tx Microcatheter System and NavAblator Ablation Catheter

Circulatory System Device Advisory Panel Meeting – May 2003

The Panel met in May 2003 to consider the application. A number of issues were highlighted in the discussion that ultimately resulted in a 7-0 unanimous decision of "NOT APPROVABLE".

1. Procedural methodology

    a. Creation of lesion sets
        i. The protocol did not define "standard" lesion set – 83% received posterolateral, posteral septal and isthmus set (90% received that set if you include those that had a prior isthmus ablation).

    b. Procedural endpoints
        i. Procedural success was defined in the protocol as demonstration of at least one of the following: reduction in the amplitude, fragmentation or widening of the local electrogram, appearance as split potentials or an increase in the pacing threshold.
        ii. These procedural endpoints were not consistently measured or recorded on the data forms
        iii. They were poorly defined with regard to RF duration, temperature goals, and amplitude reduction specifics and they were poorly measured during clinical trial.
        iv. No conclusion could be made regarding the acute procedural success.

    c. Use of multiple catheters in individual patients
        i. All linear RA non-isthmus lesions were made with the Revelation catheter. Isthmus block frequently required multiple catheters. Only 70 of 108 pts achieved isthmus block with protocol catheters. Overall isthmus block rate 84%.

2. Endpoint assessment - Primary effectiveness endpoint
    a. Defined as the reduction in symptomatic episodes of atrial fibrillation assessed six months post-procedure compared with the patient's baseline frequency.
    b. For subjects with greater than or equal to five episodes, they were required to have a 50 percent reduction. For subject with three to four episodes, they

Cardima Revelation Tx Microcatheter System and NavAblator Ablation Catheter were required to have a 75 percent reduction. These reductions were to occur in patients taking the same or a reduced dose of medication

c. How many reached primary effectiveness endpoint? 42 of 88 (42%) but this calls successful even those pts that did not make the required number of transmissions.
d. Bias
    i. Pre-procedure
        1. Patients knew a certain number of episodes were required in order to be enrolled in study – although they did not know the precise number.
    ii. Post-procedure
        1. during the six month post-procedure time period, patients were supposed to transmit recording when they were symptomatic and transmit weekly recording whether or not they were symptomatic
        2. close to 2/3 of patients did not make the minimum number of transmissions
        3. EKGs and office visits were used to try to get f/u

3. Safety
    a. 5/116 pts had a major complication within 1 week
    b. 3 pacemakers were implanted within 2 weeks
    c. 20 (23%) PM during the course of the study (9 following AV Node ablation)
    d. Initial anterior line dropped from the protocol – other lines "remote" from sinus node

P020039/A006

This Amendment contained additional information intended to support device approval. Intial device trials were as follows:

Phase IIa – Feasibility 10 pts
Phase IIb – Expanded Feasibility 38 pts
Phase III – Pivotal 82 pts

Phase IIb and III submitted to support marketing application to Panel.
P020039/A006

- Focuses on Phase 3 trial
- States that "An additional 36 pts are included". That should be 82 + 36 = 118 but they state that total number of pts is 98. In reality, it appears that data from an additional 16 patients was included. The remainder of the Amendment contains reanalysis of data and some additional data on the original study patients.
- Addresses issues of:
    - Subject compliance

- Determination of whether episodes were discrete
- Protocol adherence with regard to lesion set, and use of non-protocol catheters, changes to antiarrhythmia medication regimen's

REVELATION Tx
98 patients
93 pts with procedure related verified data
88 reached 6 month endpoint
84 form "effectiveness" cohort
"NO LOST TO FOLLOW UP"

Per sponsor:
49/84 (58%) achieved target level decrease in "monthly symptomatic AF episodes" from baseline to 6 months

47 pts (56%) has target level reduction in symptomatic AF episodes at 6 months not attributable to AV Node ablation, PM placement, or AAD changes "clinical success"

Issues outlined in June 26, 2003 FDA Not Approvable letter and Addressed in Sponsor January 21, 2004 Amendment 6 response:

Lack of accurate measurement of effectiveness endpoints

Primary endpoint defined as "reduction in frequency of symptomatic episodes of AFIB during the 6th month of follow-up compared to baseline frequency"

Lack of patient compliance

1) during the six month post-procedure time period, patients were supposed to transmit recording when they were symptomatic and transmit weekly recording whether or not they were symptomatic
2) In panel submission - close to 2/3 of patients did not make the minimum number of transmissions
3) EKGs and office visits were used to try to get f/u

The sponsor has resubmitted data on the 98 pts now comprising the Phase III group. They note that 71% of patients provided 4 or more transmissions and 82% provided 3 or more transmissions during the 6th month of follow-up. Page 95/293: 9/84 (10.7%) 3 transmissions during month 6, 65/84 (77.4%) 4 or more transmissions

I was UNABLE to determine the number of patients that were compliant with the originally designed protocol

Failure to clearly define a method to determine if symptomatic episodes reported by the pt represent discrete episodes of AFIB

Page 104/203
Sensitivity analysis not counting recurrent episodes within 24 hours of each other suggest that this "over-reporting" of a single AF episode as more than one episode did not significantly affect the results.

Lack of consistently defined procedural endpoint

1) procedural success was defined in the protocol as demonstration of at least one of the following: reduction in the amplitude, fragmentation or widening of the local electrogram, appearance as split potentials or an increase in the pacing threshold.

2) these procedural endpoints were not consistently measured or recorded on the data forms

3) poorly defined with regard to RF duration, temperature goals, amplitude reduction specifics and poorly measured during clinical trial re: how many patients actually reached these endpoints (that were not explicitly defined in the protocol)

I agree with the sponsor's statement in their letter dated 1/20/04 that "there is no universally accepted acute procedural endpoint in AF ablation". While that is true, that does not mean that a clinical study submitted to support device approval does not require well-defined acute procedural endpoints. As discussed extensively at the Panel meeting, this clinical study had poorly defined endpoints that were not consistently measured.

Page 82/293
The sponsor states that 78% of procedures had pre and post ablation paired electrode egm amplitude measurements. Therefore in 22% of the procedures, no acute amplitude change endpoints were measured. There should be 196 data points per RF electrode (98 patients x 2 lines - posterolateral and septal). The data presented shows 41-58 data points per electrode (i.e. over 2/3 of the data is missing).

The lack of a consistently defined endpoint remains a SIGNFICIANT ISSUE that is not adequately addressed by the resubmission.

Lack of complete adherence to the investigational protocol by all investigators at all investigational sites with respect to: 1) performance of the same ablation procedure with the investigational device and 2) initial attempted use of the investigational device system catheter only.

The protocol did not define "standard" lesion set – In Panel submitted data, 83% received posterolateral, posteral septal and isthmus set (90% received that set if you include those that had a prior isthmus ablation) - therefore it seems reasonable to group patients and consider outcome as a whole.

Sponsor claims (Page 5, 1/20/04 letter) "all subjects received target lesion sets recommended in the protocol". Table 37 Page 89/293 seems to confirm this.

Isthmus lesions placed with non-protocol catheters in 27/89.
23/85 cases in which study catheters were used, bi-directional block could not be achieved with study catheter alone

<u>The clinical study results are potentially biased by changes to patient antiarrhythmic medications</u>

Panel PMA: 26 patients had AAD added or increased

The resubmission notes that 3 subjects had dose increases in AAD and 12 subjects started a new AAD (this does not include patients who may have had rate controlling medications increased which could affect frequency of AF symptoms in and of itself). The sponsor submits a number of different analyses to "explain away" the AAD drug changes – in short, these pts should be counted as treatment failures.

<u>The clinical study did not contain careful characterization of the study population in terms of pre-existing comorbidities, such as sinus node function…</u>

While it would have been ideal to have additional demographic information collected for the study participants, there is adequate information to identify the intended pt population for the device/procedure.

<u>The lack of a control arm made the trial vulnerable to biases and artifacts</u>

I agree that a randomized controlled trial would make data interpretation easier. However, patients can serve as their own controls in a "before-after" study design. This type of trial design, however, is subject to significant biases that MUST be minimized with rigorous trial design and conduct.

Many biases can be eliminated or at least minimized with objective "hard" endpoints. Unfortunately, this study design had a "soft" endpoint i.e. patients were asked to make transmissions when they felt symptoms. I do not agree with the sponsor that the subjects "cannot be subject to a placebo affect". This study design and endpoint determination is quite subject to a significant placebo affect. In addition, the significant patient non-compliance with their event monitoring complicates data interpretation.

I agree with the sponsor that a randomized trial with a control arm is "not necessarily require(d)". However, a before-after study trial must have a design less susceptible to bias.

<u>Comments RE: DCD's proposed clinical trial</u>

1. While a control group that undergoes a "sham" procedure is ideal in theory, there is great debate about the ethics of performing sham procedures. Even if IRBs approved such a protocol (which I doubt), physicians would be hesitant to enroll their patients (and patients would be hesitant to enroll themselves) into such a trial.
2. Alternative trial designs could be considered. For example, a trial of afib patients randomized to ablation vs. medical management could be considered. Such a trial design is subject to potential biases and therefore, the endpoints (both procedural and clinical) and the methodology must be explicitly defined AND FOLLOWED. "Harder" endpoints (such as occurrence of afib in 1 year) with explicitly defined monitoring protocols would need to be designed to minimize bias.

CONCLUSIONS

1. Based on the unresolved significant issues discussed above, the additional information submitted in Amendment 6 does not alter the "Not Approvable" conclusion reached at the Panel Meeting of May 2003.

2. The data submitted can be utilized to support a portion of the marketing application. Specifically, the data on safety/complications could still be utilized. It should be noted, that the sponsor would be advised to take note of the specific concerns re: the high rate of post-ablation pacemaker implantation and consider supplying additional data to clarify this important issue.