

APPENDIX C

ISTHMUS ABLATION AND THE NAVABLATOR®

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

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The PMA under consideration includes a system of devices used during the clinical study. The system includes two catheters, the REVELATION[®] Tx Microcatheter, which was designed to create continuous RF lesions in the right atrium and is intended for use as a means for controlling the symptoms of atrial fibrillation (AF), and the optionally available NAVABLATOR[®] single tip catheter, which was designed as a general ablation catheter. In the REVELATION[®] Tx Microcatheter Ablation System Phase III clinical trial, physicians could use the NAVABLATOR[®], or other catheters, to ablate the cavotricuspid isthmus as prophylaxis against the occurrence of atrial flutter, a distinct disease entity.

The Sponsor developed the pivotal trial to evaluate the safety and effectiveness of the REVELATION[®] Tx Microcatheter Ablation System for the creation of continuous RF lesions in the right atrium. However, because patients undergoing catheter ablation in the right atrium were perceived to be at increased risk for atrial flutter, physician advisors recommended additional ablation of the cavotricuspid isthmus in order to prevent atrial flutter. At the time, ablation of the cavotricuspid isthmus was accepted as standard treatment for atrial flutter. However, in 1998 when the trial was designed and 2000, when the trial began, no single-tip catheter had been approved for ablation to treat or prevent atrial flutter. The Sponsor was thus unable to identify any specific catheter for isthmus ablation during the pivotal trial.

In the Phase IIb trial, investigators were instructed to use the catheter of their choice to ablate the isthmus. In the Phase III trial, physicians were first to attempt the isthmus line using the REVELATION[®] Tx Microcatheter, and had the option of using the NAVABLATOR[®] if they could not create achieve the procedural endpoint. Specifically, on page 23, the protocol specified:

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

Because three catheters¹ are now FDA approved for use in ablating the isthmus, it is unimportant to specify the NAVABLATOR[®] for isthmus ablation, and any approved catheter for isthmus ablation could be used with the REVELATION[®] Tx Microcatheter Ablation System when it is approved.

As explained in greater detail in the attached letter Cardima sent to FDA on August 16, 2004 isthmus ablation is not a valid treatment for AF, and is performed exclusively to prevent atrial flutter. In sum, the performance of the REVELATION[®] Tx Microcatheter Ablation System in treating symptoms of AF is not dependent on the use of the NAVABLATOR[®].

¹ Irvine Biomedical, Inc. IBI Therapy[™] Cardiac Ablation System (P040014); Biosense Webster, Inc. Biosense Webster NaviStar[™]/Celsius[™] ThermoCool[®] Diagnostic/Ablation Deflectable Tip Catheters (P030031); and Boston Scientific Corporation Blazer II XP[™] Cardiac Ablation Catheter, EPT-1000 XP[™] Cardiac Ablation Controller (with software version 3.12) (P020025).

Attachment to APPENDIX C

Letter from Cardima to Drs. Tillman and Yustein (FDA)

August 16, 2004



CONFIDENTIAL

This submission and its attachments are part of a PMA and constitute trade secret and confidential commercial information.

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August 16, 2004

Re: REVELATION Tx PMA and Isthmus Ablation

Dear Dr. Tillman and Dr. Yustein:

This letter is a follow-up to our meeting of August 5, 2004 in which we discussed removing both REVELATION Tx and NavAblator as catheters with which to ablate the cavotricuspid isthmus for atrial flutter from our PMA application. At this point, we are seeking PMA approval only for REVELATION Tx for the creation of continuous lesions in the right atrium for the treatment of atrial fibrillation.

The purpose of this letter is to provide background information on atrial flutter, isthmus ablation, and their relationship to atrial fibrillation. In addition, we would like to clarify a comment made at the August 5, 2004 regarding the maze procedure and the isthmus lesion. We believe the available data and information support the following observations:

1. Isthmus ablation is an effective treatment for atrial flutter.
2. Isthmus ablation is not an effective treatment for atrial fibrillation.
3. Atrial fibrillation is common after isthmus ablation for atrial flutter; thus isthmus ablation alone is unlikely to be an effective treatment for atrial fibrillation
4. Addition of isthmus ablation to lesions created to treat atrial fibrillation does not cause a further reduction in atrial fibrillation.
5. As stated during our meeting of August 5, 2004, the maze procedure does not include incision and repair of the cavotricuspid isthmus. However, it does include an incision that extends from the posterior right atrium to the tricuspid annulus.

- This lesion may result in a similar functional outcome to isthmus ablation, i.e., prevention of atrial flutter.
6. Analysis of data from the REVELATION Tx clinical trial provided no evidence that isthmus ablation affected success rates for atrial fibrillation.
 7. In the Cardima study, ablation of the isthmus may have been helpful to prevent atrial flutter. However, isthmus ablation was highly unlikely to have reduced atrial fibrillation. Moreover, patients in this study did not have atrial flutter and atrial flutter was not an outcome of the clinical study.
 8. The effect of the Cardima study system in reducing atrial fibrillation in its clinical trial patients occurred due to the creation of ablation lesions in the right atrium from the inferior vena cava to superior vena cava along the lateral and septal sides of the atrium.

A more complete discussion of these issues follows below. In the appendix to this letter, I have provided full-text copies of most of the articles cited. Please do not hesitate to call me with any questions about these articles.

Review of Atrial Flutter and Isthmus Ablation

1. **Isthmus ablation is not part of the maze procedure.** First, I'd like to clarify a statement made by Bill Wheeler at our meeting of August 5, 2004. The surgical maze procedure does not include ablation of the cavotricuspid isthmus. This is probably because stenosis of the inferior vena cava might have important health implications for the patient. However, the maze procedure does include an incision from the posterior right atrium to the tricuspid valve. Functionally, this incision may result in the same physiologic effect as isthmus ablation: blocking the large re-entrant pathway that is seen in typical atrial flutter.
2. **Treatment of atrial fibrillation with an antiarrhythmic drug (AAD) can result in atrial flutter.** This phenomenon is often called "Ic-induced flutter" since it typically this occurs with a type Ic^a AAD (e.g., flecainide, propafenone). The AAD is thought to cause the abnormal, reentrant wavelets in the heart to become more organized around a large circuit with a cycle length of approximately 250 ms. The narrowest part of this circuit is thought to involve the lower part of the right atrium near the cavotricuspid isthmus; this area is commonly called the subeustachian isthmus.² Re-entrant flow of electricity around the circuit results in atrial flutter, which shows on an EKG as rapid (approximately 220 to 400 times per minute) "flutter" waves. Depending on the proportion of flutter waves that conduct through to the ventricles, the heart rate can be high and very bothersome. Rate-control drugs (e.g., beta blockers) can slow the ventricular response rate, but do not convert the heart back to normal sinus rhythm. Figure 1 shows a rhythm strip commonly observed in atrial flutter. In this case, only one of four flutter waves conducts to the ventricle.

^a Ic refers to one of the classes of the Vaughan-Williams classification system for antiarrhythmic drugs.¹

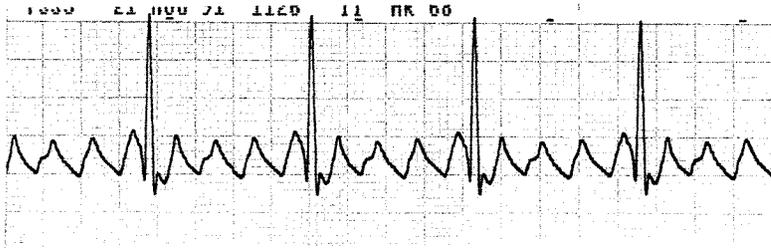


Figure 1. Rhythm strip showing atrial flutter.

3. **Atrial flutter can occur independent of antiarrhythmic drugs.** Although antiarrhythmic drugs can cause atrial flutter in patients with atrial fibrillation, they are not required. Many patients (with or without atrial fibrillation) develop atrial flutter without receiving antiarrhythmic drugs.
4. **Atrial flutter can occur in a “typical” and “atypical” fashion.** Typical atrial flutter commonly results from a counterclockwise movement of electricity in the heart. Clockwise movement is less common. Atypical flutter uses other circuits in the heart. Only typical atrial flutter is thought to respond to isthmus ablation.
5. **In patients with typical atrial flutter, isthmus ablation reduces flutter.** Many clinical studies have documented that in patients with typical atrial flutter, ablation of isthmus in the right atrium with a single-tip catheter can reduce atrial flutter. The largest multicenter study is Feld et al, in which Boston Scientific’s Blazer XP 8- or 10-mm single-tip ablation catheter was used to ablate the isthmus in 169 subjects with atrial flutter.³ One hundred twelve of 158 subjects showed absence of atrial flutter at six months of follow-up. Ablation of the isthmus for treatment of atrial flutter appears to be common practice in the US and overseas.
6. **Treatment of Ic-induced atrial flutter with isthmus ablation reduces atrial flutter.** Several studies of “hybrid” therapy for atrial fibrillation have been published.⁴⁻⁹ Hybrid therapy refers to treatment of Ic-induced atrial flutter with isthmus ablation.
7. **In patients with atrial flutter who undergo isthmus ablation, atrial fibrillation often occurs.** Among 333 Chinese patients with atrial flutter, 31% who underwent isthmus ablation for atrial flutter had atrial fibrillation in follow-up.¹⁰ Among Italian patients undergoing isthmus ablation for atrial flutter, 41% had atrial fibrillation in follow-up.¹¹ In the Blazer XP study, more than 20 of 158 subjects had arrhythmias (mostly atrial fibrillation) in follow-up. Clearly, isthmus ablation alone does not treat or prevent atrial fibrillation.
8. **If atrial fibrillation is present before ablation for typical atrial flutter, atrial fibrillation recurrence is much more likely.** Reithman followed 90 patients with drug-induced atrial flutter who underwent isthmus ablation.¹² Of these 27% had recurrent atrial fibrillation. Pre-ablation atrial fibrillation was associated with a 7-fold increase in the odds of recurrence. The high recurrence rate, along with the fact that atrial fibrillation itself is a strong risk factor, suggests that isthmus ablation is not effective for atrial fibrillation. The author concluded that hybrid therapy (antiarrhythmic drugs plus isthmus ablation) can be considered as the first

line therapy for patients with antiarrhythmic drug-induced atrial flutter but “patients should be carefully evaluated for accompanying pre-ablation episodes of atrial fibrillation ... before initiation of hybrid therapy.” This author clearly believes that isthmus ablation alone is ineffective for atrial fibrillation.

9. **Isthmus ablation alone is not used to treat atrial fibrillation.** Recent Medline searches, as well as our experience in the past six years in the field of atrial fibrillation, have shown no evidence that ablation of the isthmus alone is an effective treatment for atrial fibrillation or is perceived by electrophysiologists as an effective treatment. There are no published studies of isthmus ablation alone for atrial fibrillation treatment. Cardima’s consulting cardiologists have told us that isthmus ablation alone is not an effective treatment for atrial fibrillation. Isthmus ablation alone for atrial fibrillation is probably ineffective because atrial fibrillation is a “global” disease; in contrast, part of the typical atrial flutter circuit is nearly universally found to go through the narrow subeustachian isthmus in the inferior right atrium, which makes ablation of this circuit effective.
10. **Addition of isthmus ablation to ablations commonly performed for atrial fibrillation does not result in improved treatment of atrial fibrillation.** Ablation of the isthmus is commonly performed in procedures involving catheter ablation for atrial fibrillation as a means of preventing atrial flutter in follow-up. However, several studies have shown no or minimal effect of isthmus ablation as a means of decreasing atrial fibrillation among subjects undergoing treatment primarily for atrial fibrillation. These studies are reviewed below. Note that all patients participating in Cardima’s clinical trial had primarily symptomatic paroxysmal atrial fibrillation. They did not undergo ablation for atrial flutter.
 - a. Wazni (Cleveland Clinic) randomized patients with atrial fibrillation to pulmonary vein ostial ablation with or without isthmus ablation.¹³ There was no difference in the post-ablation survival time to recurrent atrial fibrillation (see Figure 2). In fact, there was more recurrence (not significant) when isthmus ablation was done.

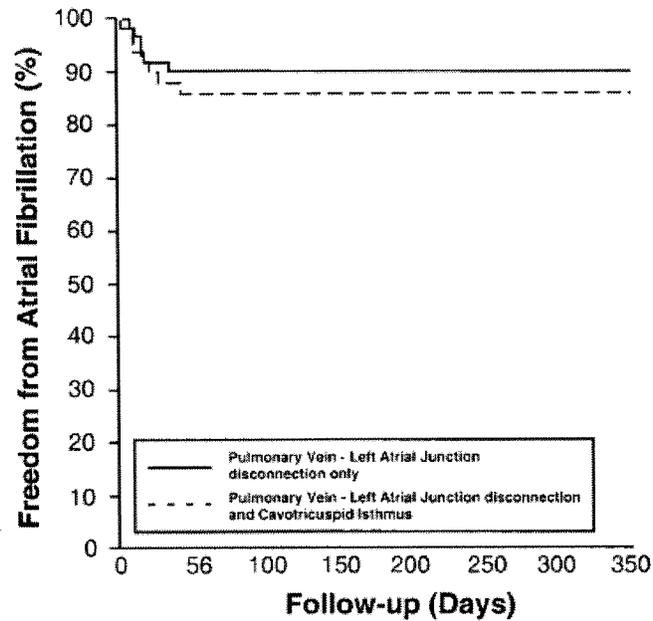


Figure 2. Freedom from recurrent atrial fibrillation after pulmonary vein ostial ablation with (dotted line) or without (solid line) cavotricuspid ablation. From Wazni et al.¹³

- b. Stabile et al randomized Italian patients with atrial fibrillation in whom intravenous flecainide induced atrial flutter to three groups:⁹
- Group A – flecainide 200 mg/day orally
 - Group B – flecainide 200 mg/day orally plus cavotricuspid ablation
 - Group C – isthmus ablation alone

In addition, patients with atrial fibrillation in whom flecainide did not induce atrial flutter were treated with flecainide in follow-up (Group D). Compared to flecainide only, flecainide plus cavotricuspid ablation helped to reduce recurrent atrial fibrillation or flutter. However, isthmus ablation alone did not improve time to arrhythmia recurrence (see Figure 3).

Moreover, isthmus ablation alone was no better than flecainide treatment among either responders (those whose atrial fibrillation was converted to atrial flutter) or flecainide non-responders.

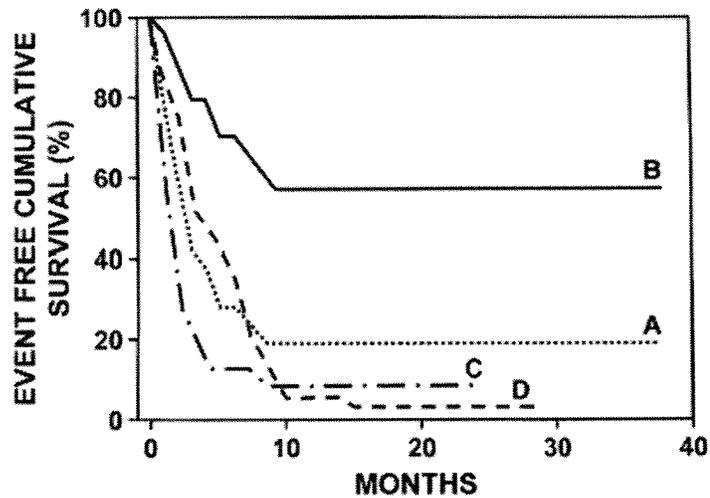


Figure 3. Time to recurrent arrhythmia in subjects randomized to Groups A to D (see text for description).⁹

- c. Haissaguerre randomly assigned patients with atrial fibrillation to ablation of the pulmonary veins either with or without mitral isthmus ablation.¹⁴ (Ablation of the mitral isthmus similarly interrupts the large circuits thought to be involved in atrial flutter; however, it is accomplished from the left atrium, not right atrium.) In follow-up, recurrence rates were very similar (74% without vs. 83% with isthmus ablation). The study did not recommend mitral ablation to increase effectiveness, and the p-value for the comparison of 74% and 83% was not provided.
- d. Scharf examined the occurrence of atrial flutter during pulmonary vein isolation for atrial fibrillation.¹⁵ Some of the patients in this study also received cavotricuspid isthmus ablation. AF recurred less often in those who underwent isthmus ablation (21%) than in those who did not (40%, $p=0.07$). However, this was not a randomized study, and the criteria by which some patients received cavotricuspid isthmus ablation vs. not receiving it were not available. This study quotes four other studies purporting to show that isthmus ablation reduces atrial fibrillation. However, most of these studies involved patients with atrial flutter.
- e. Montenero performed right atrial ablation with and without isthmus ablation in 21 patients with atrial fibrillation.¹⁶ Atrial fibrillation recurrence rates were 66% and 40% in subjects who did and did not undergo isthmus ablation. However, this was a non-randomized study. The first 15 subjects did not receive the isthmus lesion and the last 9 did. This introduces a potential timing bias on top of non-randomization bias.

In summary, three randomized studies^{9,13,14} showed no effect of isthmus ablation on reducing atrial fibrillation episodes in follow-up in patients with atrial fibrillation, and two other studies (one non-randomized) provided unconvincing data.

11. **Not ablating the isthmus in a left-atrial surgical maze procedure results in recurrent atrial flutter.** Usui reported 4 patients in 41 (10%) who underwent a left-sided only surgical maze procedure and had post-operative atrial flutter.¹⁷ These patients were effectively treated with isthmus ablation. The authors recommended isthmus ablation during a left-sided only maze procedure in order to prevent atrial flutter.

Finally, some data from the REVELATION Tx clinical trial specifically regarding isthmus ablation may be helpful.

1. **Patients did not have active atrial flutter** – Note that 24 subjects who underwent ablation had had previous ablations for atrial flutter. Only three of 93 patients had atrial flutter on a baseline EKG, and only 12 of 93 (13%) had one or more episodes of atrial flutter during the baseline monitoring period. Primarily, this patient population had atrial fibrillation.
2. **Achieving bidirectional conduction block did not improve atrial fibrillation control** – Bidirectional conduction block (BDC) is an acute procedural outcome for isthmus ablation for atrial flutter. It is well-accepted that achieving BDC during an isthmus ablation is a good predictor of long-term control of atrial flutter. In our study, BDC was demonstrated in 74 of 89 (83%) subjects in whom isthmus ablation was attempted.^c Among 81 of these subjects with six-month follow-up, success rates were actually higher when BDC was not achieved than when it was (see Table 1). This strongly suggests that blocking the cavotricuspid isthmus was not relevant to improving atrial fibrillation.

Table 1. Success rates at six months by whether bidirectional conduction block achieved (taken from Table 35 of PMA amendment of January 2004).

Bidirectional conduction block achieved	N	Success Rate (%)
No	16	87.5
Yes	65	50.8
Total	81*	58.0

*Excludes 3 subjects in whom no attempt at ablating the isthmus was made, since these patients had had isthmus ablation previously.

3. **Catheter combination used for isthmus ablation did not affect success rates** – Finally, Table 2 shows that use of NavAblator, or NavAblator followed by another catheter when BDC was not achieved, did not result in long-term success rates that were different from that achieved in all patients. Success rates were slightly higher when REVELATION Tx was used alone and slightly less when other catheters were used. However, differences are not statistically significant

^c Six subjects had previous isthmus ablation; the protocol did not require a repeat ablation, though it was mostly done.

and are based on small sample sizes. Fundamentally, there were no differences in success rate by which catheter was used to ablate the cavotricuspid isthmus. This is to be expected, since isthmus ablation has not been shown to improve control of atrial fibrillation.

Table 2. Success rates at six months by isthmus catheter(s) used to ablate the cavotricuspid isthmus (taken from table 35 of PMA amendment of January 2004).

Isthmus catheter used	N	Success Rate (%)
NavAblator	45	53.3
NavAblator then Other	18	61.1
REVELATION Tx	8	87.5
REVELATION Tx then NavAblator	2	50.0
REVELATION Tx then NavAblator then other	2	50.0
Other	4	25.0
Total	79*	57.0

*Excludes 5 subjects in whom no attempt at ablating the isthmus was made, since these patients had had isthmus ablation previously.

- Atrial flutter during baseline period did not affect success rates** – Eleven subjects had one or more episodes of atrial flutter during the baseline monitoring period and the remaining 73 did not. Success rates at 3 and 6 months after the procedure were not higher in subjects who had atrial flutter. At six months, success rates were nearly identical. These data show that the presence of atrial flutter did not affect long-term success rates. Success was not “generated” by the treatment of atrial flutter somehow reducing atrial fibrillation.

Table 3. Success rates by atrial flutter at baseline.

		Success Rate (%)	
Any atrial flutter in baseline 30 day monitoring	N	Month 3	Month 6
No	73	65.8	58.9
Yes	11	45.5	54.5
Total	84	63.1	58.3

The review above demonstrates that removal of REVELATION Tx and NavAblator for isthmus ablation is unlikely to reduce the effect of catheter ablation with REVELATION Tx in the right atrium for the treatment of atrial fibrillation. This proposal is consistent with Dr. Tillman’s suggestion at the July 8, 2002 pre-PMA meeting that Cardima consider “pooling” the catheters used to ablate the isthmus line, both as a matter of analyzing the data and in the instructions for use. Cardima agreed to that suggestion at the meeting, but in light of the fact that FDA has since approved two catheters for isthmus ablation to treat atrial flutter, it may be that FDA would prefer that the instructions for use refer to approved products rather than to the more general concept of pooling.

I hope that the above information is useful in considering our PMA application. If you have any questions, please call me or email me at the number/email listed below.

Sincerely,

A handwritten signature in black ink that reads "Daniel Cher". The signature is written in a cursive style with a large initial 'D' and a long, sweeping underline.

Daniel Cher, MD
Medical Director
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