

Circulatory System Devices Panel Questions

May 29, 2003

P020039

Cardima, Inc.

Revelation™ Tx and NavAblator™ Ablation Catheter System

Study Design and Execution

The sponsor conducted a single-arm, multi-center study. The study protocol identified three linear ablation lesions to be performed with an optional fourth lesion. The Indications for Use statement is based on the procedure dictated in the study protocol.

1. The sponsor presented acute procedural data on 116 patients, all of whom had the posterolateral and posteroseptal linear lesions performed with the Revelation Tx catheter. The tricuspid isthmus lesion was made with a variety of catheters throughout the two phases of the study (refer to the table below, retrieved from Table A-19 of submission).

Devices used to create tricuspid isthmus lesion

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

- a. Please discuss how the multiple catheter combinations affect the conclusions that may be drawn from this study.
 - b. Please discuss the ability to analyze the device outcomes versus treatment outcomes in this study. In particular, can you comment on whether the safety and effectiveness results for this study may be attributable to one specific catheter? Do the treatment strategies employed in the study support the proposed indications for use statement?
2. The study identified the acute procedural effectiveness endpoints as demonstration of either reduction in the amplitude, fragmentation or widening of local electrograms or appearance of split potentials. These endpoints were not consistently measured and/or recorded in the data collection forms. The sponsor indicated in the PMA submission that no conclusion can be made about the acute procedural success endpoint. It is unknown what measurement or electrogram characteristic was used by the individual investigator to determine when the linear lesion was completed. Therefore, each investigator may have performed a slightly different ablation procedure.
 - a. Please discuss how the lack of a measurable procedural endpoint affects data analysis for this clinical trial.
 - b. Please discuss whether the study provides sufficient information to instruct the user of the catheter system as to procedural goals or endpoints when treating an individual patient.

3. The primary effectiveness endpoint was based on comparing number of atrial fibrillation episodes captured and transmitted by event recorders during a baseline period and the 6th month post procedure in patients on the same medication or a reduced dosage.
 - a. It is unknown if each transmission represented a discrete atrial fibrillation episode. Given that the patients knew that a certain amount of episodes were required to be admitted into the study, please discuss the potential problems with accuracy in the counting of episodes at baseline and at follow up.
 - b. During the 6th month post procedure, the protocol required patients to transmit weekly recordings and, in addition, whenever they had symptoms of atrial fibrillation. Fifty three out of 83 patients (63.9%) transmitted fewer than four times in the 6th month; thus, 36.1% of patients completely complied with the protocol requirement. Please discuss how incomplete compliance with transmissions of rhythm strips impacts measurement of the primary effectiveness endpoint.

Safety

4. The safety endpoint was listed as incidence of adverse events over 24 months and major complications that occurred in the first 7 days post procedure. A total of 5/116 (4.3%, with the upper limit of a 95% confidence interval being 9.4%) patients had a major complication within a week of the right atrial ablation procedure. If all patients who required pacing within two weeks are included, the major complication rate would be 6.9% (8/116), with the upper limit of a 95% confidence interval being 13.0%. Please comment on whether the results of the clinical study provide reasonable assurance of safety for the intended use.
5. A total of 20/88 (22.7%) patients had a permanent pacemaker implanted during the long-term follow-up period. Nine of the 20 also had an AV node ablation procedure. In this patient population, please comment on whether this rate of permanent pacemaker implantation represents a significant safety concern for the device. Given the lack of a control group, please comment on how one would determine an acceptable rate of permanent pacemaker implantation.

Effectiveness

6. The primary effectiveness hypothesis was “subjects with ≥ 5 episodes during the 30 day baseline period, a reduction of 50% or more is required to constitute a clinical success. For those subjects with 3-4 episodes during the baseline period, a reduction of 75% is required to constitute a clinical success.” These reductions were to occur in patients either on the same medication regimen or decreased dosage. The results of the clinical study have been described in the presentation.
 - a. Do the clinical data provide a reasonable assurance of effectiveness of the system?
 - b. Please discuss the clinical utility of the primary endpoint of a percent decrease in atrial fibrillation episodes, as opposed to a cure for paroxysmal atrial fibrillation. Does a significant decrease in PAF episodes constitute adequate evidence for effectiveness?
7. A secondary effectiveness endpoint of the study was improvement in quality of life. Given the potential bias introduced with a non-randomized unblinded study, please comment on the device system's demonstration of improvement in quality of life.

8. If you believe that additional data are necessary to demonstrate reasonable assurance of safety and effectiveness of the Cardima ablation system, please address the following questions:
 - a. Please clarify if additional analyses on the current data set may be performed to provide adequate information to support safety and effectiveness.
 - b. Please comment if the collection of additional data using the current patient selection criteria and outcome measures would be adequate to support safety and effectiveness.
 - c. Please comment if a new prospective trial is needed to provide adequate information to support safety and effectiveness.

Labeling

9. Labeling for a new device should indicate which patients are appropriate for treatment, should identify potential device-related adverse events, and should explain how the device should be used to optimize its risk/benefit profile. If you recommend device approval, please address the following:

- a. Does the Indications for Use, as stated below, adequately define the patient population and procedural use for which the device will be marketed?

"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.

- b. Based on the study results, please discuss whether the proposed warnings, precautions, and contraindications are acceptable.
- c. Please discuss whether the instructions for use adequately describe how the device should be used.