

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

REBUTTAL OF FDA ISSUES

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1.0 POTENTIAL BIASES DUE TO STUDY DESIGN

1.1 Placebo Effect

It was suggested that, in the absence of a concurrent, blinded control group, the observed treatment effect (58% of subjects having a 6-month decrease of 50% or more from baseline, 35% of subjects having a complete elimination of AF at 6 months) cannot be separated from “placebo effect.”

Cardima Response

All episodes of AF were documented by cardiac event monitoring and verified by an independent cardiologist. Episodes that were not AF were excluded. The change in episode frequency required to be considered a success was high (at least 50%, 75% if the baseline episode count was 4 or 5). Changes in episode counts were correlated with AFSS scores and other subjective evaluations. The natural history of paroxysmal AF is well-known: it does not resolve spontaneously and often progresses.

The before-after design used in the Cardima trial, though not containing a control arm, represents a type of external control. External controls are appropriate when the subject’s condition is well-documented and the signs and symptoms are predictable, which was the case for the enrolled subjects. The before-after design was also recommended by FDA in a guidance document about AF ablation trials published in 2004.

Placebo effect, if it were to occur, would likely be limited to a few months after the procedure. Long-term duration of the placebo effect is highly unlikely; its effect would not last to 12 months if the effectiveness demonstrated was only caused by the placebo effect. In the Cardima trial, effectiveness was demonstrated at 6 and 12 months. Lastly, with a known mechanism for the effectiveness of the right-atrium ablation (based on the Cox-Maze, which routinely includes right atrial ablation), it cannot be presumed that effectiveness results from a placebo effect.

1.2 Regression to the Mean

Subjects with a low episode frequency (less than the qualifying threshold) may have qualified with 3 or more episodes due to chance or a “bad month.” Their next month would have been better due to regression to the mean (RTM).

Cardima Response

The mean number of baseline episodes (9) was far higher than the qualification threshold (3). Therefore, the expected effect of regression to the mean is very small. Computer simulation modeling presented by Dr. Cher at the June 10, 2005 meeting with FDA showed that RTM, were it to have taken place in the Cardima study, would in fact have had no effect on the success rate of the study, given the nature of the study outcome (percent decrease in episodes).

FDA indicated during the June 10, 2005 meeting that this concern had been resolved.

2.0 COUNTING AF EPISODES

2.1 Definition of Discrete Episodes

Subjects could have “split” single underlying runs of AF at baseline and “lumped” underlying runs of AF at follow-up, generating a study bias.

Cardima Response

At the suggestion of the Division, Cardima performed a detailed sensitivity analysis, provided in PMA/A006, in which it was assumed that subjects were incorrect when they reported two episodes close together; rather, we assumed that only one episode actually occurred. (Note that it is well known that paroxysmal AF episodes can occur within minutes of each other.) The close reporting of two episodes was rare; more importantly, it occurred equally at baseline and 6 months. Thus, an objective sensitivity analysis showed no effect of this proposed bias.

2.2 Corroboration Between Self-Reported AF and Clinical Outcome

It is known that some subjects may experience AF without symptoms. FDA is concerned that episodes of asymptomatic AF may not be reduced using the REVELATION[®] Tx Microcatheter Ablation System.

Cardima Response

Asymptomatic AF is not a target of treatment with the REVELATION[®] Tx Microcatheter Ablation System. The catheter was designed to reduce the frequency of symptomatic AF episodes and the endpoint is defined by the subject (symptoms), not electrocardiographically. The discussion should focus on whether treatment with the REVELATION[®] Tx Microcatheter Ablation System accomplished its stated goal, the reduction of frequency of symptomatic AF episodes.

Subjects in the Phase III trial had dealt with symptomatic AF episodes for an average of 5 years. They had taken on average 2.9 AADs prior to enrollment. They had monitored symptoms for a 30-day period prior to ablation with the study catheter. These subjects were not only very familiar with their disease, but also quite accurate in reporting symptoms. All patient-transmitted rhythm strips were confirmed by an independent cardiologist.

Cardima presented data showing that the proportion of reported symptomatic events at baseline and 6 months that were AF on examination by the cardiologist was approximately 75%. Further, when patients transmitted scheduled strips (asymptomatic), they were not in AF approximately 84% of the time. These data provide strong evidence that subjects were not selectively underreporting symptomatic episodes.

2.3 Compliance with Reporting Episodes

An event monitor was used to measure episodes of AF in the clinical trial. As a compliance maneuver, the subjects were asked to record and transmit a rhythm strip using the same event monitor on a weekly basis even in the absence of symptoms. FDA is concerned that poor compliance with this maneuver may indicate that subjects failed to report symptomatic episodes.

Cardima Response

Data presented by Cardima several times to the review team showed that non-compliance with the scheduled weekly transmission did not translate to an improved success rate. That is, the study did not “non-comply” its way into success. Rather, non-compliance with the scheduled transmissions occurred primarily among study failures. The success rate among those with higher levels of compliance was substantially higher at 74%. We conclude that our reporting of an overall success rate was not biased upwards by “non-compliance.”

2.4 Threshold for Inclusion in Trial

Subjects knew the threshold number of symptomatic AF episodes required to qualify for participation in the study and such knowledge generated a study bias.

Cardima Response

Patients participating in this clinical study knew they had to have symptomatic AF in order to enter a trial of treatment of symptomatic AF. However, the protocol stated that subjects were not to be made aware of the qualifying number of episodes. No evidence was ever brought forward to suggest that patients were aware, during the baseline recording phase, of the number of episodes required to qualify; the informed consent form used during the study does not mention the threshold number of episodes required for study enrollment. Moreover, during all monitoring periods in the study, episode interpretation by the independent cardiologist was not relayed back to subjects. Thus, it would have been difficult, if not impossible, for subjects to count the number of episodes that were, in fact, electrocardiographically proven AF.

The mean number of episodes for trial qualification was nine (9); it is unreasonable to assert that subjects reporting this many episodes somehow exaggerated their episode frequency just to get into an experimental study.

2.5 Hypothetical Concern: Overreporting at Baseline, Underreporting at 6 Months

Subjects could have “overreported” episodes at baseline (due to a desire to gain access to the trial’s experimental treatment) and “underreported” at follow-up.

Cardima Response

It is equally possible that subjects’ behavior was exactly the opposite. It is more likely that if any over- or underreporting occurred, it was similar across all time points.

The concept of “overreporting and underreporting” is an important misconception of AF episodes and represents a fundamental mistrust by the Division of study subjects themselves. The Division’s theory, that a subject somehow “expanded” his reporting of a single underlying run of AF at baseline and “contracted” such reporting at follow-up, is not based on evidence. More importantly, however, this discussion seems irrelevant, since episodes are not defined electrocardiographically, but rather by the subject. If the subject experienced a run of AF that generated no symptoms, then the subject did not have an episode of symptomatic AF. Similarly, if the subject had a single underlying run of AF, but experienced two distinct periods of symptomatic AF, such an experience represents two episodes.

In the end, Cardima believes that the theoretical underpinnings of FDA’s concern in this area are incorrect. The goal of the trial was to determine whether subjects experienced fewer episodes of symptomatic arrhythmia. We therefore asked subjects to document all symptomatic episodes; moreover, all symptomatic episodes were confirmed with a cardiac event monitor. Episode counts decreased from baseline to follow-up. The underlying precise electrocardiographic status at any particular point in time is irrelevant. What matters is what subjects actually experience from a symptomatic perspective.

3.0 ACUTE PROCEDURAL ENDPOINT

There was no acute procedural endpoint that was consistently measured and that can provide the basis for adequate instructions for use.

Cardima Response

As confirmed by the July 1998 expert panel meeting, there is no acute physiologic change that occurs following the creation of continuous lesions in the right atrium for treating AF. Other suggested endpoints (e.g., exit/entry block, bidirectional conduction block, inducibility, pacing threshold, etc.) are not relevant to right atrium ablation for AF.

In lieu of this, atrial amplitudes, a common measure of cardiac muscle ablation, were recorded. Recordings occurred in 87% of the procedures and demonstrated a mean atrial wave amplitude reduction of 56%.

This measurement represents ample evidence of ablation of cardiac tissue for the trained practitioner and provides the basis for adequate instructions for use.

4.0 OTHER SCIENTIFIC QUESTIONS

4.1 Use of Antiarrhythmic Drugs

Any changes or increases to AADs should be considered failures and should not be counted as successes.

Cardima Response

The patients enrolled in this trial were drug-refractory and had to have failed at least two AADs per the study protocol. The average number of AADs taken by patients was 2.9. There is no evidence to suggest that any of the patients became “drug successes,” and therefore, changes or increases to AADs are highly unlikely to have had any impact on the study results. Some medication changes were made due to drug intolerances or interactions. Some of the medication changes could be avoided today due to greater knowledge of the phenomenon of early post-ablation AF recurrences and due to the current 3-month blanking period practice. Finally, if 12 of the 49 patient successes who had new AADs were counted as failures, the trial success rate is still 44%.