FINAL
FDA Questions for Circulatory System Devices Panel

Atritech WATCHMAN® LAA Closure Technology (P080022)

April 23, 2009

1. Evaluation of Effectiveness

Primary effectiveness was evaluated using Bayesian methods and a cumulative patient-year design, where the primary effectiveness endpoint was defined as "successful treatment of the randomized patient without stroke (including ischemic and hemorrhagic), cardiovascular death (cardiovascular and unexplained) and systemic embolism."

Q1. Key primary effectiveness results for the updated 900 patient-year dataset are shown in Tables 1 and 2. Do these data, in addition to the original 600 patient-year data, provide a reasonable assurance that the WATCHMAN device can be used as an effective alternative to standard warfarin treatment for reduction of stroke, death, and systemic embolization? Please discuss the confounding effect of adjunctive antithrombotic drugs that were given to patients in the device arm of the trial.

Table 1: Primary Effectiveness Endpoint (ITT) 900 pt-yr data

Device			Control			Rel Risk (RR*) (95% CI*)	Posterior Prob.	
N pts	N Events / Total Pt-yrs	Rate**	N pts	N Events / Total Pt-yrs	Rate**		Non-inferiority#	Superiority
463 900 pt-yr	20/582.3	3.4 (2.1, 5.2)	244	16/318.0	5.0 (2.8, 7.6)	0.68 (0.37, 1.41)	0.998	0.837

* CI is credible interval. RR is the relative risk of device over control.
** Rate = event rate per 100 patient years (calculated as 100*N events/total patient-years).
# Non-inferiority delta = 2 X control rate

Table 2: Event Rates for Components of the Primary Effectiveness Endpoint (ITT).

Type	900-patient-year dataset			
	Device		Control	
	N Events	% of Randomized patients	N Events	% of Randomized patients
Stroke – Ischemic	14	3.0	5	2.0
Death (Cardiovascular or unexplained)	3	0.6	5	2.0
Stroke – Hemorrhagic	1	0.2	6	2.5
Systemic Embolism	2	0.4	0	0.0

2007-4/3461-03

2. Evaluation of Safety

The primary composite safety endpoint was defined as "the treatment of the patient without the occurrence of life-threatening events as determined by the Clinical Events Committee. These events included, but were not limited to, device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion and any bleeding related to the device or procedure that necessitated operation." There was no prespecified hypothesis for the primary safety endpoint and this endpoint mainly assessed periprocedural events.

Q2. Do the data provided from the PROTECT AF study provide a reasonable assurance of safety? In your discussion, please specifically comment on the incidence and significance of the pericardial effusions associated with use of this device. Please also comment on the incidence of device embolization and thrombus present on the device.

3. Training program

Q3. The pivotal trial demonstrated that qualified physicians need to carefully place this device in order to minimize acute procedural complications. Is the applicant's proposed training program adequate for training a new set of physicians in this procedure?

4. Indications for Use

The applicant has proposed the following indications for use:

"The WATCHMAN® Left Atrial Appendage (LAA) Closure Technology is intended as an alternative to warfarin therapy for patients with non-valvular atrial fibrillation. The WATCHMAN LAA Closure Technology is designed to prevent embolization of thrombi that may form in the LAA, thereby preventing the occurrence of ischemic stroke and systemic thromboembolism."

Q4. Please comment whether the proposed INDICATIONS FOR USE statement appropriately identifies the patient population evaluated in this study.

5. Labeling

One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must identify which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize clinical benefit and minimize adverse events. Please address the following questions regarding the applicant's proposed product labeling. Please refer to FDA's Executive Summary and the proposed Instructions for Use in the Panel Package for further information.

Q5a. Please comment on the CONTRAINDICATIONS section as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.

Q5b. Please comment on the WARNING/PRECAUTIONS section as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

Q5c. Please comment on the OPERATOR'S INSTRUCTIONS as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

Q5d. Please comment on the remainder of the labeling as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

Note: Question 6 is intended for Advisory Panel discussion to guide the Agency in the event that the subject device is approved by the Agency. The fact that this question is included should not be interpreted that the Agency has made a decision or a recommendation on the approvability of this device.

6. Post-Market Evaluation

If FDA should approve this PMA, several questions remain unanswered which might be addressed in an appropriate post-approval study (PAS).

The sponsor's Post Market plans consist of two parts: Post-Approval Physician Education and Training and a Post-Approval Registries Proposal. With regard to the latter, the applicant proposed two Post-Approval Studies (PAS). The first study includes follow-up of PROTECT AF study patients who received the device for 5 years. The second study includes a new prospective registry of 300 patients with plans to monitor procedural and device-related complications occurring in these patients through 45 days. The proposed study will include up to 200 patients enrolled in the currently ongoing Continued Access PROTECT AF Registry and a minimum of 100 patients enrolled in 10 new (non-PROTECT AF) centers, who do not have prior experience with the WATCHMAN device.

Q6a. Please comment on the appropriateness of the proposed Post-Approval Studies to assess the short-term and long-term safety and effectiveness of the device in real world use. This should include a discussion of the proposed endpoints, length of follow-up, and choice of study population.

Q6b. Please discuss if there is need for a Post-Approval Study to evaluate the implanting physician's experience and its effect on the performance of the device.