

Questions for Discussion

Circulatory System Devices Panel

CardioSEAL® STARFlex™ Septal Occlusion System with Qwik Load P000049/S3

September 10, 2002

Evaluation of Safety and Effectiveness

The sponsor has submitted data to support the approval of the use of the CardioSEAL® STARFlex™ device in the following patient population:

patients at risk for a recurrent cryptogenic stroke or transient ischemic attack (TIA) due to presumed paradoxical embolism through a patent foramen ovale (PFO) and, who are poor candidates for surgery or conventional drug therapy

To support this indication, the sponsor has provided a retrospective subset analysis from a registry study sponsored by Boston Children's Hospital that includes patients with various anatomic defects who are considered high risk for surgical closure. The pivotal cohort is comprised of 49 patients with PFOs.

Efficacy

1. No pre-specified outcome measures were provided for assessment of effectiveness (clinical benefit). Procedural Success defined as reduction of embolic risk using echocardiography (surrogate endpoint) has been proposed as the primary efficacy outcome measure for assessment of clinical benefit. The sponsor reports a procedural success rate of 97.7% (43 of 44 patients). Of the 49 enrolled patients, no echo information was available for 5 patients (no echo follow-up (2); echos classified by core lab as uncertain (3)). Of the remaining 44 patients, 6 additional patients are classified as having complete closure based on preliminary review (core lab readings are uncertain). See Table C.1.a in Section 5.D.1 of the Panel Pack.

Evaluation of recurrent neurological events (clinical endpoint) has been proposed as a secondary outcome measure for assessment of clinical benefit. There were no strokes reported and 4 of 49 patients (8.2%) were reported to have transient neurological symptoms. See Tables C.2.a - C.3.a in Section 5.D.1 of the Panel Pack.

- a. **Please discuss the use of "Procedural Success" as the primary efficacy outcome measure for assessment of clinical benefit.**
- b. **Please discuss the use of the occurrence of potential embolic neurological events after device placement as a secondary efficacy outcome measure for assessment of clinical benefit.**

Safety

2. No pre-specified outcome measures were provided for assessment of safety (clinical benefit versus risk). The primary safety outcome was assessed by evaluating the number of patients who experienced serious or moderately serious device, implantation, or catheterization-related adverse events. Of the 49 patients evaluated over the follow-up period, 13 patients (27%) experienced a serious or moderately serious adverse event. These events were further categorized as related to the device (n=7) or related to the implantation or

catheterization procedure (N=6). There were no patient deaths or strokes during the follow-up period. See Tables B.1 - B.13 in Section 5.D.1 of the Panel Pack.

- a. **Please discuss the use of “Serious and Moderately Serious Adverse Events” (that were definitely, probably or possibly related to the device, implantation or catheterization procedure) as the primary safety outcome measure for assessment of clinical benefit versus risk.**
 - b. **Please discuss whether the echocardiographic evaluation and clinical evaluation (including the definitions for occurrence of neurological events) allow adequate assessment of device-related clinical events.**
 - c. **Please discuss whether adequate information has been provided to allow assessment of the risk of recurrent cryptogenic stroke versus the risk of device-related neurological events.**
 - d. **Please discuss whether adequate information has been provided to characterize the appropriate post-device placement antiplatelet regimen (duration and single versus combination therapy) or anticoagulation regimen (duration and target INR).**
3. **Please comment on the lack of a pre-specified control group, pre-specified outcome measures, and pre-specified sample size.**
4. **If you believe that the data presented today are inadequate to support safety and effectiveness, please address the following questions:**
- a. **Please clarify if additional analyses on the current data set could be performed to provide adequate information to support safety and effectiveness.**
 - b. **Please clarify if the collection of additional data using the current patient selection criteria and outcome measures would be adequate to support safety and effectiveness.**
 - c. **Alternatively, if you believe that a new trial is required, please address the following clinical trial design questions:**
 - i. **Given our current understanding of the causal relationship of the presence of PFO and stroke (presumed paradoxical embolism), please discuss whether a randomized trial is necessary to evaluate safety and effectiveness. If so,**
 1. **Can a randomized trial be completed at this time?**
 2. **What is an appropriate control group?**
 - ii. **Please discuss whether adequate trials can be designed with historical controls or objective performance criteria.**
 - iii. **Based on the type of study design proposed, please address the following issues:**
 1. **Please characterize the appropriate patient population for study enrollment.**
 2. **Please discuss the appropriate primary and secondary outcome measures for evaluation of effectiveness and safety. As part of this discussion, please comment on the use of clinical versus surrogate endpoints.**
 3. **Please discuss the appropriate duration of patient follow-up.**
 4. **Please comment on what would be a clinically relevant sample size.**
 5. **Please discuss the criteria for a successful trial.**
 6. **Please comment on whether adjunctive antithrombotic medication regimens should be left to the operator or prospectively outlined in the protocol.**

Training Program

A summary of the Physician Training Program has been provided in the Section 5 of the Panel Package.

5. Please discuss any improvements that could be made to the training program.

Product Labeling

6. One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must indicate 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 benefits and minimize adverse effects. Please address the following questions regarding the product labeling (Section 2).

- a. Please comment on the INDICATIONS FOR USE section as to whether it identifies the appropriate patient populations for treatment with this device.**
- b. 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.**
- c. 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.**
- d. 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.**
- e. Please comment on the remainder of the device labeling as to whether it adequately describe how the device should be used to maximize benefits and minimize adverse events.**

Post-Market Evaluation

The Panel Package includes the available data for the STARFlex™ device in the pivotal cohort. In addition, data were provided from the ClamShell I Follow-Up study (Section 5.D.3) and include some follow-up out to 10 years. Please discuss long term adverse effects that may be associated with device implantation including late thrombosis formation, the risk of endocarditis, problems with late operation, and arrhythmias.

7. Based on the clinical data provided in the Panel Package, do you believe that additional follow-up data or post market studies are necessary to evaluate the chronic effects of the implantation of the STARFlex™ device. If so, how long should patients be followed and what endpoints and adverse events should be measured?