

FDA Summaries

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

September 10, 2002

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1.0 Lead Reviewer & Engineering Summary

Date: August 9, 2002

From: Donna Buckley, Mechanical Engineer
CDRH/ODE/DCD/ICDB

Subject: P000049/S3 - CardioSEAL® STARFlex Septal Occlusion System with QwikLoad™ -Engineering Review

1.1 PMA Chronology

April 26, 2002 – P000049/S3 received by CDRH/ODE

June 12, 2002 – PMA filed (filing letter attached)

July 30, 2002 – 90-day status letter sent to sponsor (letter attached)

September 10, 2002 – PMA scheduled for review by Circulatory Systems Devices Panel

1.2 Summary

This PMA supplement has been submitted in order to seek marketing approval for the CardioSEAL® STARFlex™ Septal Occlusion System with QwikLoad™. The device is indicated for “the closure of patent foramen ovale (PFO) in patients at risk for recurrent cryptogenic stroke or transient ischemic attack (TIA) due to presumed paradoxical embolism through a PFO and who are poor candidates for surgery or conventional drug therapy.” An earlier model of the device, the CardioSEAL® device, is currently approved under a Humanitarian Device Exemptions (HDE) application (H990011) for a similar indication: “for closure of patent foramen ovale (PFO) in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO and who have failed conventional drug therapy.” (Note that the HDE application is a limited marketing application for a Humanitarian Use Device (HUD), which is a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States per year. An HDE is exempt from the effectiveness requirements of a PMA and includes additional requirements (e.g., IRB review and approval, amount charged for the device is not to exceed the costs of research and development, fabrication, and distribution).)

The “pivotal cohort” of patients used to support PMA approval was generated from patients enrolled in the “Multicenter Trial to Study the Bard Clamshell II/CardioSEAL® Septal Occluder in High Risk Patients,” sponsored by Boston Children’s Hospital (IDE G930120). The current report of this ongoing study includes patients with various anatomic defects enrolled between 5/14/96 and 9/1/01 at six participating institutions. All patients enrolled in this study were considered to be high-risk for surgical closure, due to either complex medical or cardiac disease. Devices used in the study were obtained from C.R Bard, Inc. (Clamshell I) and from Nitinol Medical Technologies, Inc. (CardioSEAL®, STARFlex™). NMT Medical is seeking approval to market only the STARFlex® device for the PFO indication in the above-specified patient population. In order to support approval, the sponsor has performed retrospective analyses of patient subsets and device types from the Boston Children’s data set.

A total of 49 enrolled patients comprise the “pivotal cohort” and consist of patients who received the STARFlex™ device for PFO closure. Indications for device placement included prior neurological event (n=39), right-to-left shunt (n=7), or both (n=3). The follow-up data collected on these patients was analyzed for closure of the PFO and for adverse events. In order to analyze the data for device efficacy, primary efficacy outcome was defined as a reduction of embolic risk as demonstrated by complete PFO closure by echocardiography. During the follow-up period (median = 6.5 months), 43 of the 44 patients (98%) who received echocardiographic assessment had complete PFO closure. In order to analyze the data for safety, the percentages of patients with serious and moderately serious adverse events were reported. Of the 49 patients evaluated over the follow-up period, 13 (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.

In addition to the pivotal cohort, the sponsor has provided a tabulation of the data collected for PFO closure using the CardioSEAL® device (N=87) and the ClamShell I device (N=47). They have also provided a tabulation of the data collected on patients who received the STARFlex™ device (N=101) for the treatment of other defects (e.g., ASD, VSD). The Clamshell I and CardioSEAL® devices are earlier models of the STARFlex™ technology. See Section 1.3-Device Description for further information regarding the evolution of the device technology.

These data provide the basis for the analyses presented in this panel pack. The clinical investigation information is summarized in the Clinical Summary and Statistical Summary provided by John E. Stuhlmuller, M.D. and Gerry Gray, Ph.D., respectively.

1.3 Device Description

The CardioSEAL® STARFlex™ Septal Occlusion System with Qwik Load consists of a permanent implant component and a delivery catheter.

The STARFlex™ device is constructed of a metal (MP35N) framework to which polyester fabric is attached. The framework is in a “double-umbrella” configuration where the two “umbrellas” sandwich the cardiac defect. Each umbrella consists of knitted polyester fabric supported by and fastened to four wire spring arms by polyester sutures. Radiopaque markers on the spring arms allow for better fluoroscopic visualization and a pin attachment is included in the center of the device for attachment to and release from the delivery system. The implant is packaged attached to a loading device, called the Qwik Load. The Qwik Load collapses the implant in order to facilitate placement inside the delivery sheath. The STARFlex™ device is similar to the CardioSEAL® device that has been previously approved to close VSDs in high risk patients (P000049). The main difference is that the STARFlex® includes a nitinol centering spring in the implant. A summary of some key product evolutions is contained in Table 1.

Evolution of Product	ClamShell I	?? Obsolete design that was manufactured by Bard ?? Arms made of 304V stainless steel ?? One joint coil per arm ?? Wire diameter = 0.010”
	CardioSEAL®	?? Arm material changed to MP35N ?? Arm configuration modified to include both an “elbow” and “wrist” coil per arm ?? Wire diameter = 0.009”
	STARFlex™	?? Added nitinol centering spring to the implant design

Table 1: Evolution of STARFlex™ Design

The implant is manufactured in 3 sizes: 23 mm, 28 mm, and 33 mm. The sponsor recommends that device sizes should be selected such that the STARFlex™ to stretched diameter defect ratio is 1.7-2.0 to 1.0.

The delivery catheter is a 10F coaxial polyurethane catheter designed specifically to facilitate attachment, loading, delivery and deployment of the occluder to the defect.

1.4 Bench Testing

Complete bench testing was conducted on the CardioSEAL® device that was approved for VSD closure in high risk patients. Additional testing that was conducted to support the addition of the nitinol centering spring in the STARFlex™ device is summarized in Table 2.

STARFLEX™ IMPLANT	STARFLEX™ IMPLANT AND DELIVERY SYSTEM
?? Self Centering Capability (n=28)	?? Simulated Use Load and Deployment
?? Centering Spring Attachment Joint Integrity (n=28)	
?? Centering Spring to Occluder Suture Attachment Tensile Strength (n=14)	

Table 2: STARFlex™ Bench Tests

The testing conducted on the STARFlex™ device indicates that the device samples performed within specification. In addition, note that fatigue testing was previously conducted on CardioSEAL® device samples; however, the fatigue resistance of the device was not demonstrated by test or analysis. Numerous device arm fractures were previously noted in implanted CardioSEAL® devices and arm fractures of the STARFlex™ devices have also been noted in several patients.

1.6 Biocompatibility Testing

The delivery system and implant for the STARFlex™ system are constructed of the same materials using the same manufacturing methods as those used for the CardioSEAL® device. The only additional component is the nitinol centering spring. In order to assess the biocompatibility of this component, testing was performed in accordance with ISO-10993, “Biological Evaluation of Medical Devices.” The following tests were conducted on the nitinol material: cytotoxicity, sensitization, intracutaneous reactivity, systemic toxicity, hemolysis, genotoxicity, muscle implant, coagulation plasma recalcification time, C3a complement activation, material mediated pyrogenicity, and thromboresistance. The results of this testing demonstrated that the catheter is non-toxic, non-hemolytic, non-mutagenic, a non-irritant, and non-pyrogenic. All test results were within an acceptable range.

1.7 Corrosion and Toxicity

Galvanic corrosion testing and a toxicity analysis was conducted and the results indicate that significant corrosion and/or toxicological problems are not expected.

1.8 Animal Testing

Two animal studies were conducted using the STARFlex™ device. The first study was an acute animal study including 13 STARFlex™ devices deployed in 10 atrial septal defects created in 6 sheep. The second study included 8 STARFlex™ devices implanted in 8 sheep and explanted at one month (n=4) and 3 months (n=4). No major safety issues were identified from the animal testing. See Table 3 for a summary of the animal testing.

PRODUCT	TEST	TEST ARTICLE	SAMPLE SIZE	ANIMAL MODEL	RESULTS
STARFlex™	Acute Animal Study	STARFlex™ Implant + FLDS Delivery System	6 sheep 13 devices	Sheep, ASD created via transseptal puncture, + balloon dilation immediately prior to implant	Device deployment, dislodgement, and retrieval was found to be adequate. Six devices were left in place occluding the defect and 5/6 were found to be in good position by gross examination. The nitinol spring was found to be broken in one animal and attributed to improper device loading.
	Chronic Animal Study	STARFlex™ Implant + FLDS Delivery System	8 sheep 8 devices	Sheep, ASD created via transseptal puncture + balloon dilation 2 wks prior to implant, explants at 1 (n=4) & 3 months (n=4)	Detailed gross and microscopic examinations indicate that the device did not result in damage to any of the cardiac structures. Problems included reports of improper device positioning and the appearance of focal endocardial fibrosis of "friction lesions."

Table 3: STARFlex™ Animal Tests

1.9 Sterility Testing and Package Integrity

The STARFlex™ device is sterilized using the same methods as the CardioSEAL® device. The CardioSEAL® and STARFlex™ devices are sterilized using a 100% ETO cycle that has been validated to achieve an SAL of 10^{-6} in accordance with ANSI/AAMI/ISO 11135-1994. Sterilization residual limits meet the requirements of ANSI/AAMI/ISO 10993-9:1995. Shipping and package tests were also conducted and all units met test acceptance criteria.

2.0 Device Failures and Malfunctions - Clinical Use

Device arm fractures were noted post implantation in 14.3% (7/49) of the STARFlex™ devices implanted in the pivotal study; however, no adverse events were attributed to the occurrence of a device arm fracture. Although, conceptually, ulceration, perforation, patch migration, and embolization, are possible consequences of fracture, these events were not noted in the pivotal data set as a result of arm fracture. With the exception of a couple short term ulcerations that appear to have been related to fractures of an earlier device model (ClamShell I), fractures do not appear to be correlated with the occurrence of adverse events for this device design. (Note that the fracture rate for the CardioSEAL® device approved under P000049 for a VSD indication had a fracture rate of 15.9%.) Finally, device implant was attempted in 49 patients and in all patients there was successful deployment of the STARFlex™ device.

2.1 Conclusions

- ?? No data have been presented that indicate a clear safety concern in the clinical setting regarding mechanical device failure or malfunction.
- ?? There have been several incidents of device fracture; however, these events do not appear to be correlated with adverse clinical outcomes. Long term outcome for the device is unknown.

2.0 Clinical Summary

Date: July 22, 2002

From: John E. Stuhlmuller, M.D.
CDRH/ODE/DCD/ICDB

Subject: NMT Medical STARFlex? Septal Occlusion System with Qwik Load
Indication for Use-Closure of Patent Foramen Ovale

2.1 Introduction

Clinical data contained in this PMA was collected between May 1996 and September 2001 under a sponsor-investigator IDE (Boston Children's Hospital, number G930210) in an open-label, single-arm, registry entitled "Multicenter Trial to Study the Bard Clamshell II/CardioSEAL Septal Occluder in High-Risk Patients".

This registry was initiated prior to the Expanded Access provisions of the Food and Drug Administration Modernization Act of 1997. The High-Risk registry investigational plan meets the criteria for individual patient access to investigational devices intended for serious diseases, also referred to as compassionate use. The criteria for compassionate use include the following:

1. A description of the patients condition and the circumstances necessitating treatment;
2. A discussion of why alternative therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition;
3. An identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient; and
4. The patient protection measures that will be followed.

In the case of the High-Risk registry, a description of the patient's condition and circumstances necessitating treatment was provided by a study investigator for review by an independent interventional cardiologist and cardiac surgeon. The independent physician review evaluated the probable risk of using the investigational device versus the probable risk from the disease or condition and whether alternative therapies were unsatisfactory. As noted in Section 5, in the event that patients were eligible for treatment in another investigational device study, patients were enrolled in that study. Consequently, patients enrolled in this registry were considered to have no other satisfactory alternative therapies. Appropriate patient protection measures were followed. Patient protection measures included IRB review of the investigational plan, patient informed consent, and patient outcome review by a Data Safety Monitoring Board (DSMB).

The patient selection criteria included the following:

- ?? Patients with one or more cardiac defects with sufficient hemodynamic derangement to warrant intervention and one of the two following criteria:
 - A type of defect that is technically difficult or impossible to close surgically, such that the surgical risks are sufficient to justify the known and potential unknown risks of the device, or
 - An overall medical condition such that the surgical risks are sufficient to justify the known and potential unknown risks of the device.
- ?? Patient exclusion criteria related primarily to device related issues such as ability to achieve vascular access, device sizing, and relationship of device to other cardiac structure such as pulmonary veins and heart valves.

2.2 Patent Foramen Ovale -Pivotal Cohort (Section 5.D.1)

2.2.1 Registry Design

The pivotal data set represents a patient subset with patent foramen ovale (PFO) enrolled for closure in the High-Risk registry using the STARFlex device. The PFO could be an isolated cardiac defect or could be associated with other cardiac defects.

Patient selection criteria are discussed above.

2.2.2 Patient Outcome Assessment

Patient outcome assessment for effectiveness was completed using the Clinical Status Scale (CSS) developed by the investigators at Boston Children's Hospital. The CSS evaluated eight nominal variables each using an ordinal scale (0 to 6). The eight nominal variables included: right to left shunt, left to right shunt, anatomical size, presence of systemic embolization, hemodynamic compromise not due to shunt, arrhythmias, pulmonary vascular resistance, and medical condition. The ordinal scale for each nominal variable was constructed so that a change in value of 1 constituted a clinically meaningful change.

	Category	0	1	2	3	4	5
1	R? L shunt	O ₂ < 75% and/or ventilator dependent	O ₂ < 80%	O ₂ < 85%	O ₂ ? 90%	O ₂ > 90%	O ₂ > 95%
2	L? R shunt	Ventilator dependent and/or intractable CHF	Heart failure with symptoms	Left ventricular volume overload, large shunt	Moderate shunt	Small shunt	Trivial or no shunt
3	Anatomic	Ventilator dependent and/or intractable CHF	VSD diameter > 70% of aortic root diameter	VSD diameter 50-70% of aortic root diameter	VSD diameter 30-50% of aortic root diameter	VSD diameter 10-30% of aortic root diameter	VSD diameter < 10% of aortic root diameter
4	Systemic embolism		Recurrent embolic events on coumadin	Recurrent embolic events, No anticoagulation	Single embolic event	Potential for embolic event	No intracardiac potential for embolic event
5	Hemodynamic compromise not due to shunt	Inotropic dependant	Severe CHF	Moderate CHF	Mild CHF	Minimal CHF	No CHF
6	Arrhythmia		Life-threatening	Difficult to control	Requiring medication	No medication	
7	Elevated PVR		PAP with PVR > 5.0	PAP with PVR > 2.0	PAP at risk for PVOD		
8	Medical Illness		Severe	Moderate/Severe	Moderate	Mild	

Patient follow-up was completed at 1, 6, 12, and 24 months after device placement. Follow-up consisted of various combinations of clinical evaluation, fluoroscopy, echocardiography, and electrocardiography.

Adverse events were broadly categorized as related to the device, implantation procedure, catheterization or unrelated to device, implantation or catheterization. They were further characterized based on their severity (serious and non-serious) and time of occurrence after device placement. The study investigators completed initial classification. The DSMB subsequently adjudicated these events and determined whether the frequency of specific events represented a safety issue.

The sponsor has proposed evaluating safety and effectiveness based on patient follow-up at 6 months. The database was closed on 9/1/01 for information contained in this PMA supplement.

2.2.3 Results

A total of 49 patients were enrolled for PFO closure using the STARFlex device. Device placement was attempted in 49 patients. Successful placement occurred in 49 patients. A prior neurological event occurred in 39 patients (80%). Right-to-left shunt occurred 7 patients (14%). Both prior neurological event and shunt occurred in 3 patients (6%).

Patient demographic information reveals that 49% were male and almost 76% were greater than 30 years of age. Significant pre-procedure arrhythmias were noted in 16%, elevated pulmonary vascular resistance in 16%, significant non-cardiac medical illness in 42%, and significant hemodynamic impairment in 2%.

One device was implanted per patient. Three device sizes were used: 23mm-18 patients (37%), 28mm-21 patients (43%) and 33mm-10 patients (20%).

Six clinical sites participated as investigational centers.

Outcome assessment for effectiveness at the 6month patient follow-up utilized an endpoint termed "Reduction of Embolic Risk" defined as complete closure by echocardiography. This study endpoint was not previously specified as an outcome measure in the High Risk Registry. Follow-up echocardiography is not available for 5 of 49 patients (10%). Echocardiograms were not completed in 2 patients (4%). Echocardiograms were considered indeterminate in 3 patients (6%) due to errors in acquisition. Follow-up echocardiography is considered by the sponsor to be available in 44 patients (90%). Errors in acquisition occurred in 6 of these patients (12%) with the results considered preliminary. Core Laboratory evaluation is available for 38 of 49 patients (78%). The data for these two groups have been combined for the 44 patients. Errors in acquisition occurred in a total of 9 of 49 patients (18%).

Probability of freedom from first occurrence of stroke or transient neurological symptoms after device placement was 94% at 1 month, 91% at 6 months and 91% at 12 months.

Adverse events occurred in 27 of the 49 patients in whom device placement was attempted. No patients died prior to 6-month follow-up.

A total of 51 adverse events were reported with 12 device-, 1 implantation-, and 6 catheterization-related.

Moderately serious or serious events occurred in 7 patients (14%). One event each in three patients is considered device related. Two patients experienced atrial fibrillation. The first patient resolved with medical treatment. The second patient developed thrombus on the device requiring surgical removal. A third patient is reported to have experienced transient neurological symptoms with thrombus on the device requiring surgical removal. Therefore, two patients had devices surgically removed for developing thrombus on the device. Air embolism occurred in 1 patient and is considered due to the implantation procedure. Catheterization related events include catheter-induced arrhythmias (2), a retroperitoneal hemorrhage and vomiting (2).

Device arm fractures were detected in 7 of 49 devices (14%). No adverse events are categorized as fracture related.

Section 5.D.1 contains the sponsor's complete report for this patient cohort.

2.3 Non-Pivotal Patient Cohorts

Information for the following patient groups has been provided as non-pivotal data:

- ?? CardioSEAL Device, High Risk Study - PFO patients (Section 5.D.2)
- ?? Clamshell I Follow-up Study – PFO patients (Section 5.D.3)
- ?? STARFlex Device, High Risk Study – Non-PFO patients (Section 5.D.4)

2.3.1 CardioSEAL Device, High Risk Registry – PFO Patients (Section 5.D.2)

This non-pivotal data set represents a patient subset with patent foramen ovale (PFO) enrolled for closure in the High-Risk registry using the CardioSEAL device. The PFO could be an isolated cardiac defect or could be associated with other cardiac defects.

A total of 87 patients were enrolled for PFO closure using the CardioSEAL device. Device placement was attempted in 87 patients. Successful placement occurred in 87 patients. A prior neurological event occurred in 55 patients (63%). Right-to-left shunt occurred in 25 patients (29%). Both prior neurological event and shunt occurred in 7 patients (8%).

Patient demographic information reveals that 46% were male and 83% were greater than 30 years of age. Significant pre-procedure arrhythmias were noted in 17%, elevated pulmonary vascular resistance in 20%, significant non-cardiac medical illness in 49%, and significant hemodynamic impairment in 6%.

One device was implanted per patient. Five device sizes were used: 17mm-2 patients (2%), 23mm-18 patients (21%), 28mm-21 patients (24%), 33mm-35 patients (40%) and 40mm-11 patients (13%).

Four clinical sites participated as investigational centers.

Outcome assessment for effectiveness at the 6month patient follow-up utilized an endpoint termed “Reduction of Embolic Risk” defined as complete closure by echocardiography. As noted above, this study endpoint was not previously specified as an outcome measure in the High Risk Registry. Follow-up echocardiography is missing for 6 of 87 patients (10%). No information is provided for the missing studies. Follow-up echocardiography is considered by the sponsor to be available in 81 of 87 patients (93%). No information has been provided regarding the occurrence of technical errors (for example, errors in acquisition) or indeterminate interpretations. Complete closure was determined to be present in 64 of 81 patients (79%). Residual right-to-left shunts were present in 17 of 81 patients (21%).

Probability of freedom from first occurrence of stroke or transient neurological symptoms after device placement was 99% at 1 month, 96% at 6 months, 92% at 12 months, and 85% at 2 years.

Adverse events occurred in 69 of the 87 patients in whom device placement was attempted. Seven patients died during follow-up. One death is considered device related. The Safety and Data Monitoring Committee adjudicated this death to be causally related to inappropriate device use. The other deaths are attributed to the patient’s underlying cardiac or medical conditions.

A total of 175 adverse events were reported with 20 device-, 2 implantation-, and 18 catheterization-related.

Moderately serious or serious events occurred in 8 patients (9%). One event each in two patients is considered device related. One patient experienced atrial fibrillation attributed to device placement. The second patient experienced device malposition. The other device related events are not considered moderately serious or serious events. Twelve moderately serious or serious events catheterization related events were noted.

Device arm fractures were detected in 22 of 87 devices (25%). No adverse events are categorized as fracture related.

Section 5.D.2 contains the sponsor’s complete report for this patient cohort.

2.3.2 Clamshell I Follow-up Study – PFO patients (Section 5.D.3)

The Clamshell I Follow-up Study database was created in 1996 for patients who had a Clamshell I device implanted at Children’s Hospital under a previous IDE study conducted by C.R. Bard or on an emergency use basis. This database contains information derived from retrospective review of patient records prior to 1996 and prospective information on late device performance obtained at the time of clinical follow-up care since that time. The database is limited to patients in which a device has been implanted.

A total of 47 patients were enrolled for PFO closure using the Clamshell I device. Device placement was attempted in 47 patients. Successful placement occurred in 47 patients. A prior neurological event occurred in 24 patients (51%). Right-to-left shunt occurred in 18 patients (38%). Both prior neurological event and shunt occurred in 5 patients (11%).

Patient demographic information reveals that 64% were male and 79% were greater than 30 years of age.

One device was implanted per patient. Device embolization with percutaneous removal and placement of a second device occurred in two patients.

Adverse events occurred in 39 of the 47 patients (83%) in whom device placement was attempted.

Thirteen patients (28%) died during follow-up. Eleven deaths were considered unrelated to the device or procedure. The cause of death is uncertain in 2 patients.

Moderately serious or serious events occurred in 6 patients (13%). Two devices were removed at 3.7 and 9 years after implantation for atrial masses leading to neurological symptoms. Four episodes of arrhythmias were categorized as possibly related to the device.

Device arm fractures were detected in 22 of 49 devices (25%). One transient neurological episode was possibly related to device arm fracture due to temporal relationship to device arm fracture.

Section 5.D.3 contains the sponsor’s complete report for this patient cohort.

2.3.3 STARFlex Device, High Risk Registry – Non-PFO Patients (Section 5.D.4)

This non-pivotal data set represents a patient subset enrolled with lesions other than PFO in the High-Risk registry using the STARFlex device. Anatomical lesions included atrial septal defects (62%), ventricular septal defects (28%) and other lesions (10%).

A total of 101 patients were enrolled. Devices were placed in 97 patients. Multiple procedures were performed in 9 patients. Multiple devices were placed in 19 patients. A total of 116 devices were implanted.

Patient demographic information reveals that 44% were male. Median age was 17.7 years with a range from 0.9 to 82.3 years.

Adverse events occurred in 62 of the 101 patients (61%) in whom device placement was attempted.

A total of 174 adverse events were reported with 16 device-, 3 implantation-, and 58 catheterization-related. Device-related events included embolization (7), device malposition (4), and arrhythmia (4). Four devices were explanted in 2 patients.

Three patients (28%) died during follow-up. One patient did not receive a device. The other patient deaths were considered unrelated to the device or procedure.

Device arm fractures were detected in 14 of 116 devices (12%).

Section 5.D.4 contains the sponsor's complete report for this patient cohort.

2.4 Fracture Analysis (Section 5.D.5)

Combining all patients in the "High-Risk" registry who received a STARFlex device, 117 of 146 patients (with 130 implanted devices) had adequate imaging for evaluation of device arm fracture. The overall fracture rate in this report is 16%. Fracture rate is related to device size and not by type of lesion in which the device was implanted. Probability of freedom from fracture was 77% at 12 months.

Combining all patients in the "High-Risk" registry who received a CardioSEAL device, 313 of 387 patients (with 374 implanted devices) had adequate imaging for evaluation of device arm fracture. The overall fracture rate in this report is 15%. Fracture rate is related to device size and type of lesion in which the device was implanted. Probability of freedom from fracture was 84% at 12 months.

For PFO closure, there was a trend towards a lower fracture rate in the STARFlex versus the CardioSEAL patient cohort.

2.5 Issues for Panel Consideration

2.5.1 Patient Selection Criteria

- a. No pre-specified definition of cryptogenic stroke was utilized.
- b. Evidence was not provided to establish a causal relationship between the presence of PFO and stroke (presumed paradoxical embolism).
 - i. Patients with more than one embolic source for stroke were eligible for study inclusion.
 - ii. Patients with concomitant primary neurological disorders were eligible for study inclusion.
- c. No information was provided on the time of index event in relation to time of device placement.
- d. No information was provided regarding contraindications to medical or surgical management as an alternative to device placement.
- e. No information was provided on criteria for failed medical or surgical management prior to device placement.

2.5.2 Outcome Measures for Evaluation of Effectiveness (clinical benefit)

- a. The study lacked pre-specified outcome measures or sample size. Specifically, the study population was derived from a High Risk Registry intended to provide device access on compassionate use basis.
- b. No control group was identified.
- c. No justification was provided for evaluating clinical benefit at 6 months after device placement.

- d. Issues related to evaluation of clinical benefit using echocardiography for primary efficacy outcome (surrogate endpoint):
 - i. Non-uniform echocardiographic evaluation.
 - ii. Variable use of transthoracic and transesophageal imaging.
 - iii. Inconsistent quantification of right-to-left shunt pre- and post-device placement (for example, contrast versus color Doppler).
 - iv. Incomplete quantification of device-related thrombus (for example, no standardized imaging protocol with gain settings and criteria for imaging artifact(s) versus thrombus).
 - v. Technical errors in echocardiographic image acquisition in 18% of patients in “pivotal” patient cohort.
 - vi. No echocardiographic image information provided on 10% of patients in “pivotal” patient cohort.
- e. Regarding assessment of neurological outcome as part of evaluation of clinical benefit:
 - i. No information was provided whether an independent neurological evaluation was completed pre-and post-device placement.
 - ii. Device placement is intended to eliminate recurrent stroke due to presumed paradoxical embolism. No justification has been provided for evaluation of stroke (clinical endpoint) as a secondary efficacy outcome as opposed to a primary efficacy outcome.
 - iii. Definitions have been provided for cerebrovascular accident (i.e., stroke), transient neurological symptoms in middle cerebral artery (MCA) distributions (i.e., classic TIA), transient visual symptoms, and other transient neurological symptoms. Inadequate justification has been provided for limiting definition of TIA to middle cerebral artery events and excluding events in other divisions of the anterior intracranial circulation and all posterior circulation events.

2.5.3 Outcome Measures for Evaluation of Safety (clinical benefit versus risk):

- a. Issues 2a-2d as they relate to the evaluation of safety (clinical benefit versus risk).
- b. Regarding the assessment of device-related clinical events as part of evaluation of risk:
 - i. No pre-specified evaluation for right atrial-related or left atrial-related clinical events due to device-related thrombus.
 - ii. Incomplete information was provided on occurrence of right atrial and left atrial device-related thrombus formation.
 - iii. Incomplete information was provided on the occurrence of clinical events due to device-related thrombus formation.
 - iv. No information was provided on risk of recurrent cryptogenic stroke versus risk of device-related neurological event.

- v. Incomplete characterization of appropriate post-device placement antiplatelet regimen (duration and single versus combination therapy) or anticoagulation regimen (duration and target INR).

3.0 Statistical Summary

Date: July 22, 2002

From: Gerry Gray, Ph.D.
CDRH/OSB/DBS/CET team

Subject: Statistical Review for NMT Medical CardioSEAL® STARFlex™ Septal Occlusion System with Qwik Load

3.1 Introduction

The foramen ovale is an opening in the septum between the right and left atria in the fetal heart that allows for circulation to bypass the non-functioning fetal lungs. Normally this opening closes shortly after birth, but in some individuals it remains patent. There is apparently some evidence, recently obtained from transesophageal echocardiography, that a patent foramen ovale (PFO) is associated with an increased risk of stroke. The proposed causal mechanism is that venous thrombus can flow through the PFO into the arterial circulation and thus potentially cause stroke.

The current standard treatment for these patients is a lifelong regimen of anticoagulation (e.g. aspirin or Coumadin). An alternative is surgical closure, which is not widely applied because of the risks involved. Both of these alternative therapies apparently produce recurrent CVA (cerebrovascular attack) and TIA rates of 5% or less.

This device consists of two disks resting on opposite sides of the PFO that are linked together by a short connecting segment. The disks consist of MP35N metal “umbrella” frames covered with polyester fabric to prevent flow through the PFO. The device is intended for “patients at risk for a recurrent cryptogenic stroke or transient ischemic attack (TIA) due to presumed paradoxical embolism through a PFO and, who are poor candidates for surgery or conventional drug therapy.” That is, for patients who have had a stroke, TIA, or embolism for which there is no explanation, and who are at high risk for surgery.

The previous generation device (called the CardioSEAL) has already received a Humanitarian Device Exemption (HDE H990011) for patients who are at risk for recurrent stroke and who have failed medical therapy. Thus it is currently available in the U.S. for up to 4000 individuals per year. The current STARFLEX device differs from the CardioSEAL by the addition of a nitinol centering spring.

The data in this submission are presented as four separate cohorts. The first three cohorts apparently come from the same IDE (G930210), namely the “High Risk Study” conducted by Boston Children’s Hospital. In the PMA submission these cohorts are called “High Risk PFO”, “High Risk non-PFO”, and “High Risk CardioSEAL”.

- ?? The “High Risk PFO” cohort (49 patients) comprise the so-called “pivotal” data.
- ?? The “High Risk CardioSEAL” cohort (87 patients), who were treated with the earlier version of the STARFLEX device, comprise the “non-pivotal” data.
- ?? The “High Risk non-PFO” cohort (101 patients) are labeled “supporting data”.
- ?? The “Clamshell I follow-up” cohort (47 patients) comprises retrospective data collected from patients from the same center who were treated with a previous device (under IDEs G880257, G890177, G880257, or G890177).

Thus, it appears that the PMA data consist of three separate portions of data from an ongoing IDE study, along with data from patients treated with an earlier device. The sponsor does not provide any summarization of results by investigative center, but it appears that data from 4 investigative centers are included in this submission.

PFO closure patients were not identified in the study protocol as particularly important. Nor was the study designed to support a PMA submission. From the clinical protocol:

“This process is designed to provide each patient with the highest chance for an optimal result, not to establish equivalent “patient groups” for statistical comparisons. Accordingly, a direct comparison of the results of surgery versus transcatheter device closure for similar patients will not be possible; results will be necessarily descriptive.”

The patient inclusion criteria are similarly vague, i.e. that the patient has “sufficient hemodynamic derangement to warrant intervention” and is at high risk for surgery.

The primary effectiveness endpoint for the PMA (Section 5.C of Panel Pack; Clinical Report, pg. 8) is “the reduction in risk for recurrent embolic events, as assessed by achievement of complete defect closure based on echocardiography.” Secondary effectiveness endpoints include the occurrence of potential embolic or neurologic events and improvement of oxygen saturation in applicable patients. For the supporting cohort the sponsor also reports changes in the Clinical Status Scale (a 6-category scale developed for the High Risk Study) and echocardiographic closure.

The Clinical Status endpoint was one of the efficacy measures defined in the clinical protocol (the other was Severity of Illness Scale). The primary effectiveness endpoint identified in this PMA is not mentioned in the protocol; it was apparently defined at a later date.

Note also that the primary effectiveness endpoint presumes that PFO closure will (clinically) significantly reduce the risk of recurrent embolic events. The sponsor does not provide justification for the use of this surrogate endpoint.

The primary safety endpoint was the rate of all serious or moderately serious device, implantation, or catheterization-related adverse events. The secondary safety outcome was the rate of all adverse events.

There were no pre-specified criteria for a “successful” study.

3.2 Control Group Issues

As acknowledged in the original protocol, there is no control group for this study, either concurrent, historical, or literature-based. Thus, I have no basis for (statistical) comparison of the results to any reference.

3.3 Sample Size and Patient Accountability

The sample size for the PMA submission is justified in terms of the width of confidence intervals expected, but not in terms of any hypotheses to be tested or criteria for a successful study. Without such criteria, I cannot agree that the sample for this study was appropriate. The original IDE protocol did not specify any sample sizes, thus it appears that the sample size justification is entirely *post hoc*.

It also appears as if the High Risk Study is an ongoing IDE at Boston Children’s Hospital. This raises several issues relating to interim analyses of clinical trials, primarily that there is no meaningful way to assign an appropriate alpha as “significant” when there is no specified stopping point. An IDE that was intended to support a PMA submission would not be approvable without addressing this issue.

There is no clear patient accounting in this submission. That is, I cannot determine the exact disposition of all patients who were enrolled in the High Risk Study.

3.4 Results

The sponsor summarizes the results of the pivotal cohort in Section I and the non-pivotal cohort in Section II of the Clinical Data Report.

The major results from these two cohorts can be summarized in Table 1.

DEVICE	STARFLEX	CARDIOSEAL
PFO closure rate	97.7% (43/44*) [88.0%, 99.9%]	73.6% (64/87) [63.0%, 82.4%]
Neurologic Symptoms (Stroke or TIA)	8.2% (4/49) [2.3%, 19.6%]	10.3% (9/87) [4.8%, 18.7%]
Stroke	0.0% (0/49) [0.0%, 7.3%]	1.1% (1/87) [0.0%, 6.2%]
Device related SAE	14.3% (7/49) [5.9%, 27.2%]	9.2% (8/87) [4.0%, 17.3%]
Any adverse event	55.1% (27/49) [40.2%, 69.3%]	79.3% (69/87) [69.3%, 87.2%]

*five patients were not evaluated

Table 1. Summary of results for PFO patients in the High Risk Study.

Entries are on a per-patient basis (percentage, counts, and 95% confidence intervals); patients with multiple events are only counted once.

The results for the remaining two cohorts are summarized in Sections III and IV of the Clinical Data Report.

3.5 Summary

The data in this PMA submission are, statistically speaking, impossible to interpret. The primary data (the “pivotal”, “non-pivotal”, and “supporting” cohorts) are from an IDE that was not intended to support a PMA submission, and thus:

- ?? Patient selection criteria are vague.
- ?? Patient accountability is lacking.
- ?? There is no control group for comparison.
- ?? There were no pre-defined criteria for a “successful” study.
- ?? There was no pre-specified sample size.
- ?? The primary endpoints were defined after the study was conducted.

In addition, the surrogate primary endpoint of PFO closure has not been justified in the sense that the causal relationship between PFO and cryptogenic stroke is still the subject of some debate.

Therefore, I would conclude that this study does not qualify as a “well controlled investigation” and any interpretation of these results would necessarily be qualitative in nature and would require considerable clinical judgment.