

**SECTION 4**  
**FDA SUMMARIES**

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## 1.0 Lead Reviewer & Engineering Summary

**Date:** August 1, 2001

**From:** Donna Buckley, Mechanical Engineer  
CDRH/ODE/DCRD/ICDB

**Subject:** Amplatzer® Septal Occluder (ASO) – Engineering Review

### 1.1 PMA Chronology

September 1, 2000	P000039 received by CDRH/ODE
October 11, 2000	P000039 filed
January 2, 2001	Letter sent to sponsor from FDA requesting additional information
February 1, 5, 26 and March 9, 2001	Response to FDA's January 2 <sup>nd</sup> letter received
March 19, 2001	FDA requested complete audit of clinical data and requested additional preclinical and clinical information
April 23, June 28, July 13, and 19, 2001	Response to FDA's March 19, 2001, letter received
September 10, 2001	P000039 Scheduled for Review by Circulatory Systems Devices Panel

### 1.2 Summary

This PMA has been submitted in order to seek marketing approval for the Amplatzer® Septal Occluder (ASO) for the treatment of: (1) atrial septal defects (ASD) in secundum position and; (2) closure of the fenestration following a Fenestrated Fontan (FF) procedure.

The pivotal cohort (“Phase IIB”) of patients used to support PMA approval was generated from patients enrolled in a nonrandomized concurrently controlled study of ASD patients and a registry of patients with Fenestrated Fontans.

#### ASD Indication

To support the ASD indication, the sponsor has submitted data from a prospective, non-randomized concurrently controlled study comparing device closure to surgical closure.

Evaluation of composite success included assessment of patients in which closure was attempted without major complication, surgical reintervention, embolization, technical failure, or a major shunt (> 2mm). The 12-month composite success rate was 85.9% (311/362) for device patients and 94.5% (146/154) for surgical control patients. At 12 months, 1.6% (7/442) of device patients and 5.2% (8/154) of control patients had major complications. Also, 98.5% (326/331) of device patients and 100% (149/149) of surgical patients had closure of the defect (defined as < 2 mm residual shunt) at 12 months.

The ASD study originally began as a randomized study comparing device closure to surgical closure (Phase IIA); however, the design was subsequently changed to a non-randomized design (Phase IIB). Following numerous reports from the sponsor regarding difficulties in completing a randomized trial for these patients, FDA held a meeting with the Circulatory System Devices Panel (October 24, 1997) to discuss trial design issues for transcatheter septal occlusion devices. During that meeting, the Panel recommended a non-randomized trial design for ASD patients. Consequently, the sponsor revised the trial design to a non-randomized design and those patients included in the non-randomized trial are the “Phase IIB” patients which comprise the pivotal cohort.

Due to rapid enrollment in the device arm of the non-randomized study compared to the surgery arm, the number of patients in the device arm was increased. After all of the surgery patients were enrolled and preliminary data were submitted for the device patients, the sponsor requested a Continued Access Study. This study was approved following review of the preliminary safety data.

Fenestrated Fontan Indication

To support the Fenestrated Fontan indication, the sponsor has submitted data from a single arm registry. The results indicate that all patients had closure of the fenestration (defined as < 2 mm shunt) at 12 months without the need for reintervention. Major complications occurred in 4.2% (2/48) of these patients.

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 Stuhlmuller, M.D., and John Dawson, respectively.

**1.3 Device Description**

The ASO device is a self-expanding, self-centering, repositionable, double-disk device comprised of nitinol (nickel-titanium alloy) metal braid and delivered percutaneously. A cylindrical waist that is selected to correspond to the size of the defect joins the two disks. The device is intended to be offered in 26 sizes ranging from 4 mm to 38 mm. Polyester patches have been sewn into the disks and waist in order to promote a thrombotic response post-placement. Platinum marker bands are attached at the apex of each disk and a microscrew attachment on the proximal disk connects the device to the delivery cable. The delivery cable is made of 304SS and contains a microscrew that is welded to the distal end for insertion into the microscrew attachment of the ASO device. A pin vise attached to the proximal end of the delivery cable is used to unscrew the ASO device from the delivery cable following deployment. The total Amplatzer system consists of the following components: (1) dilator, (2) loading device, (3) delivery cable, (4) plastic pin vise, (5) sizing plate, (6) ASO device, and (7) delivery sheath (6F to 12F) with side arm and hemostasis valve.

The sponsor has also requested approval for an Exchange System that is intended to aid in the removal of an Amplatzer device in the event that the delivery catheter kinks or fails in some way. The Exchange system is comprised of the same materials and design as the delivery catheter with the exception that the dilator has a larger inner lumen to allow for passage over the delivery cables. The Exchange System will be offered in two sizes (9F and 12F) and will be sold separately. (Note that the Exchange System was not used in the clinical trial.)

**1.4 Bench Testing**

The bench tests conducted using finished, sterilized devices, are summarized in Table 1.

IMPLANT	DELIVERY SYSTEM
<ul style="list-style-type: none"> <li>• Pull Test, Laser Welds – Marker Bands to Wire Braid and Screw Attachment to Marker Bands</li> <li>• Pull Test, Delivery Cable – Delivery Cable Screw and Device End Screw</li> <li>• Device Integrity</li> <li>• Cycle Testing</li> <li>• MRI compatibility</li> <li>• Corrosion</li> </ul>	<ul style="list-style-type: none"> <li>• Delivery Sheath Kink Resistance</li> <li>• Delivery Cable Kink Resistance</li> <li>• Pull Tests, Delivery Sheath, Hub to Tubing</li> <li>• Pull Test – Delivery Cable, Cable to Cable Screw Weld Joint</li> </ul>

**Table 1: Bench Testing**

The testing conducted indicates that the device samples tested performed within specification. In addition, shelf life testing was conducted to support a three year shelf life. The conclusion from the fatigue and corrosion testing is that there is no clear evidence that the device will fail due to fatigue and there was no gross evidence of corrosion in the samples tested. Although this is the case and rigorous fatigue testing was

conducted by the sponsor, fatigue failure, perhaps facilitated by corrosion, is always a concern given that there is no ideal *in vitro* model to simulate the *in vivo* environment and that the *in vitro* testing only models a 12-year implant period for a device that has the potential to be implanted over a lifetime. No wire fractures have been reported in devices implanted in patients.

## 1.5 Biocompatibility Testing

Biocompatibility tests in accordance with ISO-10993, “Biological Evaluation of Medical Devices”, were conducted on the Implant and the Delivery Catheters. Test results indicate that the device system is biocompatible. A summary of the tests conducted is included in Table 2.

TESTS CONDUCTED	DELIVERY SYSTEM	POLYESTER MATERIAL IN IMPLANT
cytotoxicity	✓	✓
sensitization	✓	✓
systemic toxicity	✓	✓
subchronic toxicity		✓
intracutaneous reactivity	✓	✓
hemolysis	✓	✓
chronic toxicity	✓	pending*
mutagenicity		✓
muscle implantation		pending*

\* Test reports for these tests are due by 8/15/01 and will be submitted to the FDA.

**Table 2: Summary of Biocompatibility Testing**

## 1.6 Animal Testing

Amplatzer ASO devices were placed in 11 swine in which an ASD had been surgically created. The created ASDs ranged in size from 8 to 16 mm. The animals were sacrificed at 7 days (N=1), 9 days (N=2), one month (N=5), three months (N=2) or four months (N=1). There was an acceptable histological response and tissue in-growth and endothelialization was complete by 1 to 3 months.

In addition, two swine were sacrificed 14 and 18 months post-implantation and devices were examined for evidence of corrosion. Evidence of corrosion or wire fracture was not seen in subsequent scanning electron microscope studies.

## 1.7 Sterility Testing and Package Integrity

The Amplatzer® ASO is 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 residuals were specified to be below acceptable maximum limits (25 ppm ethylene glycol, 25 ppm ethylene chlorohydrin, and 50 ppm ethylene glycol).

## 1.8 Device Failures and Malfunctions - Clinical Use

There were six device procedural failures in 1.41% (6/424) of patients enrolled in the ASD trial. In three cases, the device embolized and required surgical removal and in three cases the sheath tip marker band embolized. In one patient, the marker band was surgically removed. In the second patient, the marker band was left in the pulmonary artery branch. In the third patient, the band was removed from the groin site. In response to these events, the sponsor removed the marker band from the 9F and 10F delivery sheaths (11/98) and subsequently from all delivery sheaths (12/99). No other significant device failures or malfunctions have been noted.

## **1.9 Conclusions**

- The incidence of device failures and malfunctions during clinical use of the Amplatzer was low. The sponsor has attempted to implement design, labeling, and training changes to help minimize the occurrence of these events.
- Although no problems with device integrity have been reported, long term outcome for the device is unknown.

## 4.0 Clinical Summary

**Date:** July 2, 2001

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

**Subject:** AGA Medical The Amplatzer® Septal Occluder System  
Indications for Use- (1) Closure of Atrial Septal Defects  
(2) Closure of Fenestrated Fontan

### 4.1 Introduction

Atrial septal defects (ASD) are congenital abnormalities of the atrial septum characterized by structural deficiency of the atrial septum in one or more locations. ASDs account for approximately 10% of all congenital heart disease. Ostium secundum defects are the most frequent type of ASD. The physiological consequences of an ASD are related to the size of the left to right shunt and response of the pulmonary vascular bed to the volume overload. ASD closure is primarily indicated for the prevention of the pulmonary vascular changes associated with volume overload.

Table 102 (Appendix III) outlines the different phases of patient enrollment. Phase I is a single-arm open-label registry. The intent of this registry was to gain operator experience with the device and evaluate the initial safety of device use. Devices were placed in 22 patients. Phase IIA was a concurrent randomized study that enrolled 38 patients. Devices were implanted in 32 patients. After initiating the randomized study, input was obtained from the Circulatory System Devices Advisory Panel in December, 1997 regarding trial design for septal occluders. The Panel felt that a non-randomized study design using a prospective concurrent surgical control arm was satisfactory.

Phase IIB is a multi-center, open-label device registry with a concurrent surgical control group. Initial sample size estimates required 130 patients each in the device and surgical arms. FDA agreed to a combination of retrospective and prospective identification of patients for the surgical arm. Patient enrollment in the device arm was completed prior to enrollment of the surgical patients. As a result, patient cohorts were sequentially enrolled in an extended investigation registry as part of the continued access provisions based on the Expanded Access provisions in the Food and Drug Administration Modernization Act of 1997. The criteria for an extended investigation include the following:

1. A justification for the extension;
2. A summary of the preliminary safety and effectiveness data generated under the IDE;
3. A brief discussion of the risk posed by the device;
4. The proposed rate of continued enrollment (the number of sites and subjects);
5. The clinical protocol, if different from that used for the controlled clinical trial, as well as the proposed objectives for the extended study; and
6. A brief discussion of the sponsor's progress in obtaining marketing approval for the device.

A total of 442 patients were enrolled in the Phase II B study. This is considered the pivotal data set for the evaluation of safety and effectiveness.

Subsequently, FDA approved a request for additional patient enrollment under the Continued Access provisions of the Expanded Access provisions noted above. A total of 465 continued access patients have been enrolled as of May 2001.

## **4.2 Pivotal Data Set for Closure of Atrial Septal Defects (Section 5.1)**

### **4.2.1 Registry Design**

The sponsor conducted a multi-center, open-label registry for the device arm. As noted above, the Phase II B registry is the pivotal device data set. The control arm consists of patients who underwent surgical closure. Patients were identified in a retrospective manner after surgery and prospectively prior to surgery. All completed a prospective 1-year follow-up evaluation.

### **4.2.2 Description of Patients**

The patient selection criteria for the device group were intended to identify patients with an isolated ostium secundum defect with evidence of volume overload on the right side of the heart. Patient inclusion was limited initially to defects with diameters of  $\leq 26$  mm and later to defects with diameters of  $\leq 38$  mm based on device sizes. Patients with pulmonary vascular resistance above 7 Woods units, other types of cardiac disease such as recent myocardial infarction, and signs of sepsis were excluded.

The patient selection criteria for the surgical group were similar with no upper size limit on the defect size or number of defects.

Assessment included clinical evaluation, echocardiography, electrocardiography, and cardiac catheterization.

Table 9 outlines patient demographic information. The mean age in the device group was 18 years of age with a range of 0.6 to 82 years of age. The mean age in the surgical group was 6 years of age with a range of 0.6 to 32 years of age.

Gender distribution was similar between the device and surgical groups (68% females in the device group and 61% in the surgical group). The surgical group had larger and multiple defects based on the differences in the patient selection criteria between the groups. Patient demographic data in this group was obtained by retrospective chart review in some cases (37) and prospectively in the rest (117). All patients required a prospective echocardiogram performed at 12 months using standardized imaging acquisition.

Overall, both patient groups demonstrated the clinical, echocardiographic, hemodynamic, and electrocardiographic characteristics associated with ASDs.

### **4.2.3 Assessment of Patient Outcome**

Patient evaluation was required at 24 hours, 6 months and 12 months after the index procedure.

### **4.2.4 24-Hour Evaluation**

Device placement was attempted in 442 of 459 patients enrolled in the device arm. Devices were successfully placed in 423 of 442 patients attempted. Overall, device placement was successful in 92% of patients enrolled in the study (423 of 459). Statistical analysis is not based on an intent to treat analysis.

Procedural variables such as procedure and fluoroscopy time are outlined in Table 16. Mean procedure time in the device arm was 106 minutes with a range of 33 to 320 minutes. Mean fluoroscopy time in the device arm was 21 minutes with a range of 3 to 116 minutes.

Table 18 indicates the number of devices used by size. Device size ranges from 4 mm to 38 mm. Devices in the range from 10 mm to 28 mm accounted for 89% of devices implanted.

Technical success was defined as successful deployment of the device or successful completion of surgery. Success rates are reported in Table 19 for patients in which device placement was attempted. Technical failure was defined as when the device was inserted and recaptured or acute embolization occurred. Reasons for technical failure were primarily related to anatomical issues based on defect characteristics such as rim or size. One acute embolization occurred.

Shunt closure defined as a residual shunt  $\leq 2$  mm was demonstrated in 413 of 423 (97.6%) patients implanted in the device arm. Shunt closure was demonstrated in 154 of 154 surgical patients.

Five device embolizations occurred. One occurred upon release from the delivery system. Three occurred within 24 hours of device placement. One occurred at 9 days after device placement. Two were removed percutaneously. Three required surgical removal. No specific clinical events were noted with the embolizations. Technical issues related to device sizing and the structural stability of the defect rim contributed to the occurrence of device embolization. Based on these events, the investigational plan was modified. A chest x-ray at one week and providing additional restrictions on patient activity for at least 1-month after device placement were added.

#### **4.2.5 6-Month Evaluation**

All device patients were scheduled to complete a clinical and imaging evaluation (echocardiogram and chest x-ray). No specific follow-up was mandated for surgical patients at this time point.

Follow-up information is provided on 389 of 416 device patients.

Shunt evaluation was completed on 387 device patients. Complete closure was demonstrated in 341 of 387 patients (88.1%). A shunt was demonstrated in 46 of 387 patients with a trivial shunt in 10 patients (2.6%), small shunt in 25 patients (6.5%), moderate shunt in 9 patients (2.3%), and large shunt in 2 patients (0.5%). Success defined as shunt  $\leq 2$  mm was demonstrated in 376 of 387 patients (97.2%; complete closure-341, trivial-10, and small-25).

No device fractures were noted.

#### **4.2.6 12-Month Evaluation**

All device and surgical patients were scheduled to complete a clinical and imaging evaluation (echocardiogram and chest x-ray).

Follow-up information is provided on 335 device and 109 surgical patients.

Shunt evaluation was completed on 331 device patients. Complete closure was demonstrated in 304 of 331 patients (91.8%). A shunt was demonstrated in 27 of 331 patients with a trivial shunt in 7 patients (2.1%), small shunt in 15 patients (4.5%), moderate shunt in 4 patients (1.2%), and large shunt in 1 patient (0.3%). Success defined as shunt  $\leq 2$  mm was demonstrated in 326 of 331 patients (98.5%; complete closure-304, trivial-7, and small-15).

All shunts were closed in 94 of 94 surgical patients completing echocardiographic evaluation.

No device fractures were noted.

### **4.2.7 Analysis of Adverse Events**

Adverse events were initially categorized as major or minor. The Data Safety Monitoring Board revised the initial classification to include major, minor, and observations.

Major adverse events were noted in 7 of 442 (1.6%) Phase IIB device patients. Major adverse events included the following: cardiac arrhythmia requiring major treatment in 2 patients (0.5%, pacemaker placement or long-term drug treatment), device embolization with surgical removal in 3 patients (0.7%), device embolization with percutaneous removal in 1 patient (0.2%), device delivery system malfunction in 1 patient (0.2%), marker band embolization requiring surgical removal).

Major adverse events were noted in 8 of 154 (5.2%) surgical patients. Major adverse events included the following: pericardial effusion with cardiac tamponade in 3 patients (1.9%), pulmonary edema in 1 patient (0.6%), repeat surgery in 2 patients (1.3%), and wound complications in 2 patients (1.3%).

Minor adverse events were noted in 27 of 442 (6.1%) Phase IIB device patients. Minor adverse events included the following: allergic reactions in 2 patients (0.5%), cardiac arrhythmias requiring minor treatment (required drug treatment) in 15 patients (3.4%), device embolization requiring percutaneous removal in 1 patient (0.2%), headaches/possible TIA in 2 patients (0.5%), %, device delivery system malfunction in 2 patients (0.5%, marker band embolization) and thrombus formation in 3 patients (0.7%).

Minor adverse events were noted in 29 of 154 (18.8%) surgical patients. Minor adverse events included the following: cardiac arrhythmias requiring minor treatment (required drug treatment) in 9 patients (5.2%), pericardotomy syndrome in 2 patients (1.3%), pericardial effusion in 6 patients (3.9%) pneumothorax in 3 patients (1.9%), and transfusion in 2 patients (1.3%).

## **4.3 Pivotal Data Set for Fenestrated Fontan Closure (Section 5.2)**

### **4.3.1 Registry Design**

The sponsor conducted a multi-center, open-label registry.

### **4.3.2 Description of Patients**

Patients with a fenestrated Fontan baffle with a clinical indication for closure were eligible for device placement. A minimum distance of 5 mm between the baffle communication and the atrial free wall and a central venous pressure less than 15 mm Hg were required.

Device placement was attempted in 48 of 51 patients enrolled in the registry. Devices were implanted in 46 of 48 patients in which device implantation was attempted. Device deployment could not be completed in 2 patients.

Table 76 outlines the patient demographic information. The mean age in the device group was 8 years of age with a range of 1.6 to 45 years of age. Gender was 60% male.

### **4.3.3 Assessment of Patient Outcome**

Patient evaluation was required at 24 hours, 6 months and 12 months after the index procedure.

Shunt evaluation was completed in 46 patients at 24 hours. Complete closure was demonstrated in 41 of 46 patients (89%). A shunt was demonstrated in 6 of 46 patients with a trivial shunt in 3 patients (6.5%) and a small shunt in 3 patients (6.5%). No moderate or large shunts were present.

Shunt evaluation was completed in 38 patients at 6 months. Complete closure was demonstrated in 35 of 38 patients (92%). A trivial shunt was demonstrated in 3 of 38 patients (8%). No small, moderate or large shunts were present.

Shunt evaluation was completed in 32 patients at 12 months. Complete closure was demonstrated in 29 of 32 patients (91%). A shunt was demonstrated in 3 of 32 patients with a trivial shunt in 1 patient (3.1%) and a small shunt in 2 patients (6.3%). No moderate or large shunts were present.

A total of 4 adverse events were noted (major and minor-2 each). The major adverse events consisted of a hemothorax requiring drainage and a tricuspid valve tear requiring valve replacement. The minor adverse events consisted of an occurrence of atrial fibrillation requiring cardioversion and persistent post-procedure nausea and vomiting requiring a second night of hospitalization.

## 5.0 Statistical Summary

**Date:** July 23, 2001

**From:** John Dawson, Mathematical Statistician  
CDRH/OSB/Division of Biostatistics

**Subject:** AMPLATZER Septal Defect Occluder, by AGA Medical Corporation (P000039/A8),  
July 18, 2001 – Statistical review

### 5.1 Introduction

All statistical concerns in my October 12, 2000 review memo on P000039 have been addressed: (1) more complete follow-up to 12 months is reported now, than in the original August 2000 PMA, (2) request for actuarial estimates of effectiveness and safety endpoints have been granted, (3) attention has been paid to differences between the device and surgical control study arms as regards age and morbidity, and (4) poolability of data across sites has been analyzed.

### 5.2 Extent of follow-up

The original PMA submission last summer reported that only about half of the device patients had been followed to 12 months. Now, as of the cutoff date of May 25, 2001 for this amendment, upwards of three-quarters of implanted patients are accounted for at 12 months, but still with some 20% who should have, but did not, have a 12 month visit.

Out of 459 patients enrolled in the AMPLATZER Septal Defect Occluder device study arm, 17 were not attempted (“Intent to Treat” cases), while the remaining 442 were attempted. Out of those 442 attempted, 423 were implanted. Here is the 12-month status of 423 implanted patients (see pages III-7 & 49):

- 331 had a 12-month visit completed
- 68 missed the visit
- 12 were lost because of IRB lapse
- 4 had the visit but without shunt assessment
- 4 were lost-to-follow-up, and
- 4 were lost because of non-acute embolizations.

Out of 155 patients enrolled as surgical control patients, all but 1 were attempted. Here is the 12-month status of 154 surgical control patients (see p. III-7):

- 109 had a 12-month visit completed
- 37 missed the visit
- 5 were lost because of IRB lapse
- 0 had the visit but without shunt assessment
- 3 were lost-to-follow-up, and

### 5.3 Statistical endpoints

In my statistical review of the PMA, I made said the that endpoints where patients’ had variable exposure times should not be computed as simple binomial proportions (or percentages). In a teleconference with the company, they pointed out that there was no variation in exposure time for the primary effectiveness

criterion -- percentage of patients at 12 months with successful shunt closure -- since the denominator only counted patients with a 12-month visit, so binomial calculations were appropriate in that case.

***Primary effectiveness endpoint:*** The primary effectiveness endpoint was residual shunt  $\leq 2$  mm at the 12-month visit, with a goal of the device-minus-surgery difference in percent of patients with effective closure (success) being no less than  $-8\%$ , as a lower 1-sided 95% confidence limit. (Protocol, pages 12 and 14) That target was used in computing the sample size goal of 110 subjects per study arm.

***Results:*** Out of 331 patients with a 12-month visit, 326 had effective closure (98.5%), compared to 100% closure success in the surgical control group. (p. III-5) The lower confidence limit on the device-minus-surgery difference is  $-5.2\%$ , so they have met the primary effectiveness criterion. In computing this confidence limit, the rates are appropriately characterized as binomial variables, since everyone evaluated at 12 months had the same duration of exposure to the risk of failure.

***Primary safety endpoint:*** “Acceptable limits” were defined in the protocol as  $\leq 2\%$  deaths and  $\leq 10\%$  major complications in the device group. (Protocol, p.14) I interpret these deterministic goals as defining the bounds of a device non-inferiority to surgery.

***Results:*** There was one death in the device group, which sponsor considers not device-related deaths; hence, the 2% mortality goal was met. The goal was also met in the case of major complication, reported on p. III-9 as 1.6%. Sponsor also undertook to compare that 1.6% with the 5.2% for surgical controls. Since time-to-complication was variable, a Cox regression analysis was done, with time-to-complication as the dependent variable. Study arm was tested as a predictor, for which sponsor reports a significant p-value: this implies a lower risk of major complication with the device. Sponsor decided there were too few events to do covariate-adjustment (i.e. testing age, etc., as predictors) in the Cox regression analysis. **The small number of events precluding covariate analysis also precludes a claim of major-complication superiority**, rather than non-inferiority, for the device. The Cox results do support a finding of non-inferiority.

#### **5.4 Possible confounding owing to age and morbidity differences**

I noted in my October review memo that device patients were on average 18 years old, compared to 6 years old in the case of surgical control patients, and also noted a difference in the device and surgical arms in percentage of cases with particular morbidities. Sponsor acknowledges these differences between the study arms (p. III-18) and has now incorporated age and morbidity as covariates in actuarial modeling, as will be discussed.

***Effectiveness – differences due to age and morbidity?:*** The possibility of confounding of differences in effectiveness with differences in age and morbidity between the study arms was analyzed on an age- and morbidity-adjusted actuarial basis (p. III-48). The effectiveness variable in this analysis was the secondary endpoint, “12 Month Composite Success”, which was met by all but 15 device and 8 surgical control patients. A composite failure meant “a major complication, [consisting of] surgical reintervention, embolization, technical failure, or major shunt...” (p. III-6) This combines both safety and effectiveness considerations, and since the safety issue is subject to variable exposure time, it needs actuarial statistical treatment. When computed on an unadjusted actuarial basis, the device and surgery rates, rounded, are 87% and 93.8%, respectively. (pages III-53 and 54) This 7% point difference is statistically significant ( $p = .043$ ). (p. III-48) But sponsor proceeded to do covariate adjustment, which they report “raised the p-value to slightly greater than 0.05.” They also add that “None of the covariates contributed significantly to the Cox regression model,” suggesting that the  $p = .043$  is the definitive result. **While sponsor makes no claim about the 12-month composite success outcome (p. III-101), it does appear that the lower rate for device (87% versus 94% for surgery) is at least borderline significant.**

***Safety:*** Sponsor provides an age-adjusted comparison of the study arms on *all* complications (minor or major), which purports to show higher incidence in the surgical control arm in all age categories (p. III-68). The actuarial complication rates were 7.5% and 26.7% for device and surgery (pages III-71 and 72).

Sponsor reports that the inclusion of covariates did not remove statistical significance. This lends weight to a claim of device superiority in the case of complications, as long as no distinction about severity is to be drawn.

## 5.5 Poolability of data

Poolability across sites, or other patient subgroups, is a particularly important issue when the device deployment requires surgical implantation, which depends on surgical skill. Site-to-site homogeneity of success rates is key to giving the device user the assurance that the overall, pooled data accurately reflect what that user can expect. Poolability across sites, both with respect to site-specific complications (minor and major), and with respect to the 12 month composite success, have been addressed by sponsor, using computer simulation. They conclude the following about site-to-site variation in 12 month rates:

*Secondary safety variable:* Difference among sites is not statistically significant as regards minor and major complications. (p. III-90)

*Secondary effectiveness variable:* Difference among sites is significant. (p. III-55) Out of the 20 sites, exactly half had a percent success above the overall 85.9% for all sites pooled, which combined accounted for 188, or 54.7% of the total 362 patients. **The practical significance of the variation in device success rates across sites should be assessed from a clinical perspective.**

## 5.6 Other issues

Sponsor indicates in Table 1 on p. III-5 some 149 surgical control patients with successful closure at 12 months, but the patient flow diagram on p. III-7 shows only 109 with a closure assessment, **an apparent inconsistency**. This does not affect the finding of success in meeting the -8% target for difference in closure rates.

Since  $68+4 = 72$  and  $37+3 = 40$  patients missed the 12-month visit or were lost to follow-up, in the device and surgical control groups, respectively, (p. III-7), intent-to-treat (ITT) analysis should be done on the primary effectiveness variable, 12-month closure, that includes these cases as assumed treatment failures as of 12 months post-treatment – i.e. added to the at-risk denominators but not to the successes in the numerators. With these changes, the primary success rate for device is now on the high side of surgical control: 80.9% versus 78.8% and the lower confidence limit on the difference, -4.1%, still satisfies the goal of no worse than -8%. **Sponsor should do an ITT analysis of the 12-month composite success data with the patients who were lost to follow-up or missed the 12-month visit treated as failures after the date of the last contact.**

I understand there is concern about patients with occluders of sizes ranging as high as 38 mm. There are too few such patients for any definitive conclusions. I would point out that of 16 device patients with occluders of sizes over 30 mm that were evaluated at 12 months, only 9 were composite success outcomes. (p. III-57) The success rate,  $9/16 = 56.2\%$ , has a wide 2-sided 95% confidence interval, 29.9% to 80.2%.

Sponsor did much the same kind of statistical analyses on Fenestrated Fontans patients as on ASD patients, though based on just 32 patients. I think this is too small a sub-study to comment on from a statistical perspective, except to observe that the effectiveness and safety results, taken at face value, are favorable. (Pages III-103 and 105)

Finally, I need to point out a minor omission: in Table 39, p. III-49: the 12-month composite success rate for AMPLATZER **was not updated**, still showing 87.6%. The 85.9% rate is correctly cited on p. III-5 and III-48.

## 5.7 Conclusion

Sponsor has shown statistical non-inferiority of AMPLATZER to surgery as regards the primary safety and effectiveness targets of, respectively, freedom from major complications and closure success at the 12-month visit. The closure success rate of 98.5% for AMPLATZER meets the confidence limit goal for establishing non-inferiority to the 100% success for the surgical controls. The major complication rate of 1.6% meets the goal of not exceeding 10%, and the difference between that 1.6% and the 5.2% for the surgical control group was found to be statistically significant. No deaths were reported in either study group. These findings are clearly favorable to the company.

On secondary endpoints of particular interest, one is favorable to the company and one is not: As to the 12-month composite success endpoint, which is a combined safety and effectiveness measure, the AMPLATZER success rate appears to be some 7% points lower than for surgical control (87% versus 93.8%), a difference that is at least borderline significant – not favorable. As to minor and major complications combined, the rates were 7.5% and 26.7% for AMPLATZER and surgery, which is statistically significant even when covariates are accounted for – clearly favorable.