

## Summary of Safety and Effectiveness Data

### 1. *General Information*

Device Generic Name: Transcatheter Cardiac Occlusion Device

Device Trade Name: AMPLATZER® Muscular VSD Occluder

Applicant's Name and Address: AGA Medical Corporation  
5050 Nathan Lane  
Plymouth, MN 55442  
USA

Date(s) of Panel Recommendation: None

PMA Number: P040040

Date of Notice of Approval: September 7, 2007

### 2. *Indications and Usage*

The AMPLATZER Muscular VSD Occluder is indicated for use in patients with a complex ventricular septal defect (VSD) of significant size to warrant closure (large volume left to right shunt, pulmonary hypertension and/or clinical symptoms of congestive heart failure) who are considered to be at high risk for standard transatrial or transarterial surgical closure based on anatomical conditions and/or based on overall medical condition.

High risk anatomical factors for transatrial or transarterial surgical closure include patients:

- Requiring left ventriculotomy or an extensive right ventriculotomy;
- With a failed previous VSD closure;
- With multiple apical and/or anterior muscular VSDs (“Swiss Cheese Septum”); or
- With posterior apical VSDs covered by trabeculae

### 3. *Contraindications*

- Patients with defects less than 4 mm distance from the semilunar (aortic and pulmonary) and atrioventricular valves (mitral and tricuspid).
- Patients with severely increased pulmonary vascular resistance above 7 woods units and a right-to-left shunt and documented irreversible pulmonary vascular disease.
- Patients with perimembranous (close to the aortic valve) VSD.
- Post-infarction VSD.
- Patients who weigh < 5.2 kg. (Patients smaller than 5.2 kg were studied in the clinical trial, but due to poor outcome these patients have been contraindicated for device placement. Data from these patients are not included in the overall analysis.)
- Patients with sepsis (local/generalized)

- Patients with active bacterial infections.
- Patients with contraindications to anti-platelet therapy.

**4. Warnings and Precautions**

See warnings and precautions in the Physician Labeling/Physician Manual and Instructions for Use.

**5. Device Description**

**AMPLATZER Muscular VSD Occluder**

The AMPLATZER Muscular VSD Occluder is a self-expandable, double disc device made from a Nitinol wire mesh. The two discs are linked together by a short cylindrical waist corresponding to the size of the Ventricular Septal Defect (VSD). In order to increase its closing ability, the discs and waist are filled with polyester fabric. The polyester fabric is securely sewn to the device by polyester thread. The device is available in multiple sizes (Table 1A).

**Table 1A: Device Specifications**

Device Order Number	Device Size (at waist)	Left and Right Ventricle Disc Diameter	Length of Connecting Waist	TorqVue Delivery System	
				45°	180°
9-VSD-MUSC-004	4 mm	9 mm	7 mm	6 Fr	5 Fr
9-VSD-MUSC-006*	6 mm	14 mm	7 mm	6 Fr	6 Fr
9-VSD-MUSC-008*	8 mm	16 mm	7 mm	6 Fr	6 Fr
9-VSD-MUSC-010*	10 mm	18 mm	7 mm	6 Fr	6 Fr
9-VSD-MUSC-012*	12 mm	20 mm	7 mm	7 Fr	7 Fr
9-VSD-MUSC-014*	14 mm	22 mm	7 mm	8 Fr	8 Fr
9-VSD-MUSC-016	16 mm	24 mm	7 mm	8 Fr	8 Fr
9-VSD-MUSC-018	18 mm	26 mm	7 mm	9 Fr	9 Fr

\*NOTE: The device specifications for the 006 – 014 devices were modified after the clinical trial was completed. The devices used during the clinical trial utilized a right ventricular disc that was 2mm smaller than the left ventricular disc. The marketed devices have equal disc diameters.

**AMPLATZER TorqVue Delivery System**

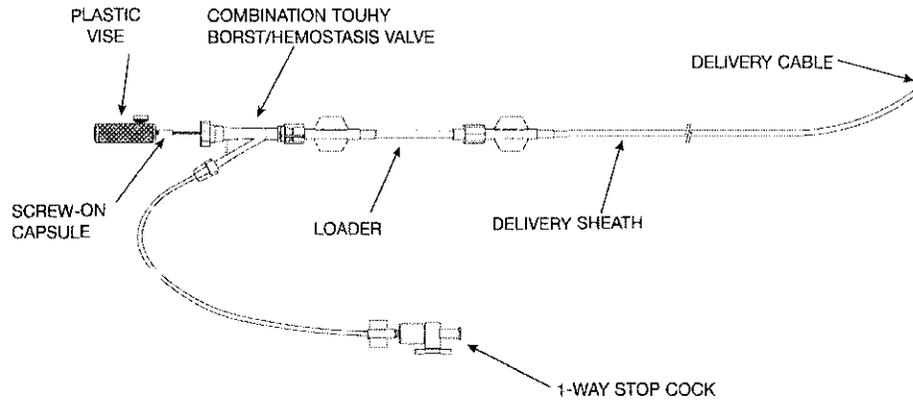
The AMPLATZER Muscular VSD Occluder is implanted with either a 45° or a 180° AMPLATZER TorqVue Delivery System. The delivery system selected is based on physician preference for sheath placement.

<i>If preferred sheath placement is</i>	<i>Select a</i>
Middle of LV	45° delivery system
Ascending aorta	180° delivery system

**Delivery System components include:**

- Delivery Sheath – used to deliver the device.
- Dilator – used to ease penetration of tissue

- Loader – used to introduce the Occluder device into the delivery sheath.
- Touhy-Borst adapter with extension tube and stopcock – used to minimize bleeding and for flushing of the system.
- Plastic Vise – facilitates direction control and serves as the “handle” for disconnecting (unscrewing) the delivery cable from the device.
- Delivery Cable – allows placement and recapture of the device.



**Figure 1 - AMPLATZER TorqVue Delivery System**

**AMPLATZER TorqVue Exchange System**

The AMPLATZER TorqVue Exchange System is intended for removal of an AMPLATZER TorqVue Delivery Sheath and subsequent exchange for an AMPLATZER Delivery Sheath of equal or larger diameter. The system components are identical to the AMPLATZER TorqVue Delivery System, with the exception of the dilator, which incorporates an enlarged inner lumen for passage over a delivery cable.

Table 1B includes the available TorqVue Delivery and Exchange Systems.

**Table 1B: TorqVue Delivery and Exchange System Descriptions**

Product Re-order Number	Product Description
9-ITV06F45/60	TorqVue 45° Delivery System: 6 French Sheath; 60 cm Length
9-ITV07F45/60	TorqVue 45° Delivery System: 7 French Sheath; 60 cm Length
9-ITV07F45/80	TorqVue 45° Delivery System: 7 French Sheath; 80 cm Length
9-ITV08F45/60	TorqVue 45° Delivery System: 8 French Sheath; 60 cm Length
9-ITV08F45/80	TorqVue 45° Delivery System: 8 French Sheath; 80 cm Length
9-ITV09F45/80	TorqVue 45° Delivery System: 9 French Sheath; 80 cm Length
9-ITV10F45/80	TorqVue 45° Delivery System: 10 French Sheath; 80 cm Length
9-ITV12F45/80	TorqVue 45° Delivery System: 12 French Sheath; 80 cm Length
9-EITV09F45/80	TorqVue 45° Exchange System: 9 French Sheath; 80 cm Length
9-EITV12F45/80	TorqVue 45° Exchange System: 12 French Sheath; 80 cm Length

Product Re-order Number	Product Description
9-ITV05F180/60	TorqVue 180° Delivery System: 5 French Sheath; 60 cm Length
9-ITV06F180/60	TorqVue 180° Delivery System: 6 French Sheath; 60 cm Length
9-ITV06F180/80	TorqVue 180° Delivery System: 6 French Sheath; 80 cm Length
9-ITV07F180/80	TorqVue 180° Delivery System: 7 French Sheath; 80 cm Length
9-ITV08F180/80	TorqVue 180° Delivery System: 8 French Sheath; 80 cm Length
9-ITV09F180/80	TorqVue 180° Delivery System: 9 French Sheath; 80 cm Length
9-EITV06F180/80	TorqVue 180° Exchange System: 6 French Sheath; 80 cm Length
9-EITV8F180/80	TorqVue 180° Exchange System: 8 French Sheath; 80 cm Length
9-EITV10F180/80	TorqVue 180° Exchange System: 10 French Sheath; 80 cm Length

## 6. *Alternative Practices or Procedures*

1. Surgical closure of Muscular VSD. A cloth patch is sewn over the VSD through an incision in the chest (open chest surgery). Later this patch is covered by the normal heart lining tissue and becomes a permanent part of the heart. Some defects can be sewn closed without a patch.
2. Treatment with a different commercially available VSD Occluder.
3. No treatment.

## 7. *Marketing History*

Commercial distribution of the AMPLATZER Muscular VSD Occluder began outside of the United States in 1999.

The AMPLATZER Muscular VSD Occluder is marketed for use in the following countries: Algeria, Argentina, Armenia, Australia, Austria, Azerbaijan, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Cuba, Cyprus, Czech Republic, Denmark, Egypt, Estonia, Finland, France, Germany, Greece, Georgia, Guatemala, Hong Kong, Hungary, Iceland, India, Ireland, Israel, Italy, Jordan, Kazakhstan, Kuwait, Kyrgyzstan, Latvia, Liechtenstein, Lithuania, Malaysia, Malta, Mexico, Moldova, Monaco, Morocco, Netherlands, New Zealand, Norway, Oman, Pakistan, Panama, Peru, Poland, Portugal, Qatar, Romania, Russia, Saudi Arabia, Singapore, Slovak Republic, Slovenia, South Africa, Spain, Sri Lanka, Sweden, Switzerland, Tunisia, Turkey, Ukraine, United Kingdom, Uruguay and Vietnam.

The AMPLATZER Muscular VSD Occluder has not been withdrawn from marketing for any reason relating to the safety or effectiveness of the device.

## 8. *Summary of Preclinical Studies*

### 8.1 Bench Testing

The muscular VSD device is manufactured using the same materials, manufacturing processes and quality controls as the approved AGA Medical Amplatzer devices (i.e., ASD Occluder (P000039), Duct Occluder (P020024) and Vascular Plug (K031810)). Non-clinical testing to support PMA approval of the VSD device includes data collected using either VSD device samples or one of the other

approved Amplatzer products. For those selected tests conducted on other device models, device performance is believed to be representative of the performance of the VSD device.

A. Withdrawal Force Testing:

The force required to withdraw the device into the specified sheath was measured for each device size. The maximum force was measured to be 5.36 lbs (14 mm device in 7 F sheath) and all devices met the specification of 5.95 lbs for the peak withdrawal force. See Table 2.

**Table 2: Withdrawal Force Testing**

VSD Size (mm)	Wire Size (in)	Sheath Size (F)	Samples	Specification	Peak Force Mean ± SD (range) lbs
4	0.003	5	2	Peak Force < 5.95 lbs.	2.28 ± 0.18 (2.15 - 2.40)
6	0.004	6	2		3.80 ± 0.07 (3.75 - 3.85)
8	0.004	6	2		3.65 ± 0.35 (3.40 - 3.90)
10	0.004	6	2		3.55 ± 0.35 (3.30 - 3.80)
12	0.005	7	2		3.55 ± 0.00 (3.55 - 3.55)
14	0.005	7	2		3.63 ± 0.04 (3.60 - 3.65)
16	0.005	7	2		3.40 ± 0.21 (3.25 - 3.55)
18	0.005	7	2		3.15 ± 0.14 (3.05 - 3.25)

B. Tensile Testing:

Tensile strength was measured between the following device components: (1) the marker band to distal apex of device referred to as “laser weld-marker band”; (2) the screw attachment to proximal apex of device referred to as “screw attachment to marker band laser weld”; and (3) the threaded connection between delivery cable screw and end screw attachment. Testing was performed on other Amplatzer device models and is representative of the performance of the Amplatzer VSD occluder. See Table 3.

**Table 3: Tensile Testing**

Test	Occluder	Wire Diameter (in)	Sample Size	Specification	Peak Force Mean ± SD (range) lbs	
Laser Weld-Marker Band	PDA	0.003	6	> 12 lbs	27.98 ± 3.69 (23.65 - 34.75)	
	ASD	0.004	9		30.34 ± 2.56 (26.30 - 35.45)	
	ASD	0.005	10		36.79 ± 3.45 (32.9 - 44.65)	
Screw Attachment – Marker Band Laser Weld	PDA	0.003	6		40.05 ± 6.41 (32.25 - 49.35)	
	ASD	0.004	5		34.8 ± 7.57 (28.25 - 45.30)	
	ASD	0.005	7		38.31 ± 5.80 (31.10 - 47.0)	
Delivery Cable Screw – Screw Attachment	N/A (components used)	N/A	5			26.37 ± 2.32 (23.35 - 29.15)

C. Design Verification Testing:

Additional Design Verification Tests were performed using samples of the equal-sized disk VSD occluders with the largest recommended VSD Occluder for each given sheath size (i.e., 10 mm, 14 mm, 18 mm device sizes). All devices tested were finished, twice sterilized and packaged product. See Table 4.

**Table 4: Design Verification Testing**

Test	Sample Size	Specification	Result
Visual Device Inspection	N= 30 for each of the 10 mm, 14 mm and 18 mm device sizes	freedom from visible defects including broken wires and loose fabric	all samples found to be free of gross defects
Retention Disk and Waist Diameters		diameters +/- 0.5 mm	all 14mm devices met specification two 10mm devices did not meet specifications seven of the 18mm devices did not meet specifications
Embolization Test <sup>1</sup>		none noted	Maximum force required to push device from block was measured and plotted. Scatter of data indicates that devices out of specification do not deviate from the general scatter of data collected for devices within specification.
Device Attachment through Delivery Sheath <sup>2</sup>		device must pass through loader easily, advancement force in midsection of delivery sheath < 5.0 lbs (with 95% confidence and 90% reliability) and device must deploy easily from distal end of sheath	1.61 lbs (10mm device, 6F sheath) 1.69 lbs (14mm device, 8F sheath) 1.60 lbs (18mm device, 8F sheath) excessive forces were measured with the 14mm device in a 7F sheath; therefore, the testing was repeated with an 8F sheath
Device Deployment into Simulated VSD		devices must deploy and expand fully in simulated defect	All devices performed as intended.
Device Retraction into Delivery Sheath <sup>3</sup>		device recaptured into sheath with < 5.0lbs force at 95% confidence and 90% reliability	4.69 lbs (10mm device, 6F sheath) 5.03 lbs (14mm device, 8F sheath) 4.29 lbs (18 mm device, 8F sheath)
Markerband to Braid Laser Weld Tensile Strength		tensile strength > 12.0 lbs at 95% confidence and 90% reliability	25.21lbs (10mm device) 34.00 lbs (14mm device) 35.37 lbs (18mm device)
End Screw to Markerband Laser Weld Tensile Strength		tensile strength > 12.0 lbs at 95% confidence and 90% reliability	28.04lbs (10mm device) 37.32 lbs (14mm device) 45.76 lbs (18mm device)

<sup>1</sup> Samples of the 10 mm and 18 mm devices sizes were not within dimensional specifications; however, there was no difference in the force required to embolize these devices through a simulated defect.

<sup>2</sup> Device Advancement through Delivery Sheath testing originally included placement of the 14 mm device with a 7F sheath; however, due to the excessive forces measured, an 8F sheath was required. Now the device size recommendations include use of an 8F sheath for devices from 12 mm to 18 mm and a 7F sheath for devices from 6 mm to 10 mm.

<sup>3</sup> The Retraction Force for the 14mm device exceeded the specification of 5.0 lbs primarily due to a single device that required 5.2 lbs force for recapture. All other devices performed within specification.

## 8.2 Magnetic Resonance Imaging (MRI) Testing

Through non-clinical testing, AMPLATZER devices have been shown to be MR Conditional (as defined in ASTM F 2503-05). A patient with an implanted AMPLATZER device can be scanned safely immediately after placement of the device under the following conditions:

- Static magnetic field of 3 T or less
- Spatial gradient magnetic field of 720 G/cm or less
- Maximum MR system-reported, whole-body-averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of scanning

During testing, the device produced a clinically non-significant temperature rise at a maximum MR system-reported, whole-body-averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of scanning in a 3-tesla MR system using a transmit/receive body coil.

## 8.3 Fatigue Testing

Cycle testing was performed using samples of the Amplatzer ASD Device with samples of the smallest and largest device sizes for each wire diameter. Thirty devices of each size were tested for a total of 240 devices. Samples were cycled greater than 440 million times (equivalent to a 12-year implantation time) which consisted of expansion of the waist to simulate septal thickening (2mm) during contraction. Following the testing, devices were examined for evidence of abrasion, pitting due to corrosion, wire fracture and loss of superplasticity. During the testing, one device (24 mm) was found to have a brass metal shaving (presumably an aberrant machine component) between the disks with multiple broken wires noted. Two additional devices (17 mm) had one broken wire, one near the end screw and the other near the marker band. None of the fractured wires were displaced and the devices appeared to retain their preset shape. Note that this information was previously reviewed under the ASD PMA (P000039) and deemed acceptable for that clinical use. Given the similarities in wire materials, wire diameters, shape and manufacturing, the results of the ASD device are believed to be representative of those of the VSD device.

## 8.4 Corrosion Testing

The potential for device corrosion was evaluated using *in vitro* and *in vivo* methods. A single device was evaluated for corrosion per ASTM F746 and no general pitting or crevice corrosion was noted. Eight devices were evaluated for corrosion using a cyclic polarization method and pitting and crevice corrosion did not occur; however, the shape of the resultant hysteresis curve suggested that localized corrosion may occur. For that reason, additional *in vivo* analysis was performed. Devices were implanted in two swine animal models for 14 and 18 months. Post-mortem evaluation of explanted device wires via Scanning Electron Microscopy (SEM) did not reveal differences in surface appearance compared with new wires. Based on this combination of testing, corrosion is not expected to be a safety concern with this device.

## 8.5 Biocompatibility Evaluation

The AMPLATZER Muscular VSD Occluder is constructed of Nitinol (a nickel-titanium alloy) and polyester using the same materials, manufacturing methods and sterilization methods as the approved Amplatzer Septal Occluder (P000039). Therefore, additional biocompatibility testing of the VSD device was not necessary.

## 8.6 Sterilization and Shelf Life Testing

### *Sterility*

The AMPLATZER Muscular VSD Occluders are sterile, single-use devices. The sterilization cycle was validated per AAMI/ANSI/ISO 11135 to ensure successful sterilization to a Sterility Assurance Level (SAL) of  $10^{-6}$ .

Ethylene oxide residual testing was performed in accordance with AAMI/ANSI/ISO 11135 and EN 550 guidelines. The results met the proposed guidelines for products intended for human use.

### *Shelf Life Tests/Packaging Tests*

Product and package stability testing of the AMPLATZER Muscular VSD Occluder was performed. Visual inspection and physical testing indicated that the device performed within product specification for up to 5 years. An expiration date of 5 years has been established.

## 8.7 Animal Testing

Animal studies were conducted to verify the feasibility of device placement and post implant closure rates. Muscular VSDs were surgically created in fourteen (14) mongrel dogs. Two dogs died during surgery due to ventricular fibrillation. One dog died four weeks after creation of the VSD before the device could be placed. In a fourth dog, the defects spontaneously closed three (3) weeks after surgical creation. A total of ten (10) dogs were implanted with the VSD device. With the animal under general anesthesia and with the use of sterile conditions the devices were implanted using one of two possible approaches (right-sided femoral approach or surgical approach). The technical success of the study was 100% (10/10) and the VSD closure rate was also 100% (9/9) at the time of the last catheterization. (Note that one dog died 3 hours after implant due to hemorrhage.) Following device placement, all animals had a Qp/Qs (i.e., ratio of pulmonic versus systemic flow) of 1 with minimal residual shunt. The evidence obtained through the pathologic examinations demonstrated tissue in-growth (endothelialization) with full incorporation of the device within the ventricular wall.

## 9. *Potential Adverse Effects of the Device on Health*

### 9.1 Clinical Summary

The AMPLATZER Muscular VSD Occluder was evaluated in a prospective, multi-center, non-randomized, controlled investigation to evaluate Muscular VSD closure. The original study included patients receiving primary treatment of VSD without establishment of a prospective statistical plan (i.e., sample size, hypotheses) to

establish safety and effectiveness. Of these consecutively enrolled patients, the clinical data presented below comprises a subset of patients retrospectively established by an independent review board to be “high risk.” Safety and effectiveness hypotheses were also retrospectively established.

## 9.2 Deaths

There were two reported deaths during the clinical trial in the High Risk patient population; both deaths were adjudicated by the Data Safety Monitoring Board (DSMB) as major adverse events.

A three year old female with multiple muscular ventricular septal defects underwent three cardiac catheterizations. Five coils and five AMPLATZER Muscular VSD Occluders were implanted during the first and third procedures. During the second procedure an attempt was made to implant an AMPLATZER Muscular VSD Occluder which was unsuccessful. Seven months after the third procedure she died suddenly. An independent DSMB adjudicated this death as a major adverse event but was unable to determine if the death was related to the procedure or the device.

A seven month old male with a large muscular ventricular septal defect and pulmonary hypertension underwent cardiac catheterization for device closure of the defect. During the procedure a device was attempted which was too small. The physician encountered difficulties in removing the device and ultimately inadvertently pulled the 10 Fr delivery sheath out of the right internal jugular vein resulting in bleeding, hypotension and cardiac arrest requiring resuscitation. The next day it was noted that the patient had suffered cerebral injury as a result of the procedural complications. The patient died three weeks post-procedure. An independent DSMB adjudicated this death as a procedure related major adverse event.

## 9.3 Observed Adverse Events

Table 1 presents the major and minor adverse events, per patient and per procedure, observed in the “high risk” patient population. As the sample size was limited, the unadjusted 95% confidence interval upper bound for any major adverse event was 60.25% per patient and 55.83% per procedure.

**Table 6: Major and Minor Adverse Events**

<b>MAJOR Adverse Event Type</b>	<b>Adverse Event Per Patient (%)</b>	<b>95% Upper Confidence Bound<sup>1</sup></b>	<b>Adverse Event Per Procedure (%)</b>	<b>95% Upper Confidence Bound<sup>1</sup></b>
Hematoma <sup>2</sup>	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Hypotension <sup>2</sup>	5/41 (12.2%)	26.20%	5/51 (9.8%)	21.41%
Bradycardia <sup>2</sup>	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Arterial pulse loss	2/41 (4.9%)	16.53%	2/51 (3.9%)	13.46%
Blood Transfusion	2/41 (4.9%)	16.53%	2/51 (3.9%)	13.46%
Subaortic stenosis	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Cardiomyopathy	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Delivery System Failure	2/41 (4.9%)	16.53%	2/51 (3.9%)	13.46%
Death	2/41 (4.9%)	16.53%	2/51 (3.9%)	13.46%
Stroke	2/41 (4.9%)	16.53%	2/51 (3.9%)	13.46%
Blood loss	4/41 (9.8%)	23.13%	4/51 (7.8%)	18.88%
Device Embolization	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Paroxysmal Ventricular Tachycardia <sup>2</sup>	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Third Degree Heart Block	2/41 (4.9%)	16.53%	2/51 (3.9%)	13.46%
Cardiac perforation	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Hemostasis and coagulation disorders	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Anemias Caused By Blood Loss	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Device Collapse	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Cardiac Arrest	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
<b>Any Major Adverse Event</b>	<b>18/41 (43.9%)</b>	<b>60.25%</b>	<b>21/51 (41.2%)</b>	<b>55.83%</b>
<b>MINOR Adverse Event Type</b>				
Hematoma <sup>2</sup>	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Hypotension <sup>2</sup>	2/41 (4.9%)	16.53%	2/51 (3.9%)	13.46%
Bradycardia <sup>2</sup>	2/41 (4.9%)	16.53%	2/51 (3.9%)	13.46%
Atelectasis	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Venous Thrombosis	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Atrial Flutter	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Stridor	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Paroxysmal Ventricular Tachycardia <sup>2</sup>	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Cyanosis	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Edema	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Premature Ventricular Contraction	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Fever	1/41 (2.4%)	12.86%	3/51 (5.9%)	16.24%
Second Degree Heart Block Mobitz Type 2	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
Vomiting	1/41 (2.4%)	12.86%	1/51 (2.0%)	10.45%
<b>Any Minor Adverse Event</b>	<b>10/41 (24.4%)</b>	<b>40.30%</b>	<b>13/51 (25.5%)</b>	<b>39.63%</b>
<b>Any Major or Minor Adverse Event</b>	<b>22/41 (53.7%)</b>	<b>69.34%</b>	<b>28/51 (54.9%)</b>	<b>68.87%</b>

<sup>1</sup> Confidence intervals are unadjusted for multiple comparisons.

<sup>2</sup> An independent data safety monitoring board reviewed and adjudicated all adverse events and depending on the severity and/or time of occurrence the same type of event could be classified as either a major or a minor adverse event.

#### 9.4 Potential Adverse Events

Placement of the AMPLATZER Muscular VSD Occluder involves using standard interventional cardiac catheterization techniques. In addition to the above observed adverse events, the following are potential adverse events listed in alphabetical order. The following events might occur from either the catheterization procedure or from the device:

**Table 7: Potential Adverse Events**

Air embolus	Fever
Allergic dye reaction	Headache/Migraine
Allergic drug reaction	Heart block
Anemia	Hypertension/Hypotension
Anesthesia reactions	Myocardial infarction
Apnea	Perforation of the vessel or myocardium
Arrhythmia	Peripheral embolism
Arterial pulse loss	Pleural Effusion
Atelectasis	Pulmonary edema
Bacterial endocarditis	Seizure
Blood loss requiring transfusion	Stridor
Brachial plexus injury	Stroke
Cardiac arrest	Subaortic stenosis
Cardiomyopathy	Thrombus formation on device
Chest pain	Valvular regurgitation
Cyanosis	Vascular access site injury
Death	Venous thrombosis
Device fracture	Vocal Cord Paralysis
Device embolization	Vomiting
Device malalignment	

## 10. **CLINICAL STUDIES**

The original study included patients receiving primary treatment of VSD without establishment of a prospective statistical plan (i.e., sample size, hypotheses) to establish safety and effectiveness. Of these consecutively enrolled patients, the clinical data presented below comprises a subset of patients retrospectively established by an independent review board to be “high risk.” Safety and effectiveness hypotheses were also retrospectively established.

### 10.1 Study Purpose

The primary purpose of this evaluation was to retrospectively determine if the AMPLATZER Muscular VSD Occluder is reasonably safe and effective for the treatment of congenital muscular ventricular septal defects in patients with complex ventricular septal defect of significant size to warrant closure who are considered to be at high risk for standard transcatheter closure based on anatomical conditions and/or based on overall medical condition.

Primary effectiveness was evaluated at 12-months post-implant. Successful closure of the defect was defined as less than or equal to 2 mm residual shunt. Effectiveness was also evaluated at 24-hours (acutely), 1-month, 6-months, and 24-months post-implant.

In addition, patients were classified according to the Clinical Status Scale pre-procedure, and 6-months and 12-months post-procedure.

Safety was assessed following device placement attempt through the follow-up period by collecting all adverse events that occurred among all consented patients.

## 10.2 Study Design

This study was a prospective, non-randomized, multi-center clinical investigation. A total of 11 investigational centers received IRB approval and enrolled patients in the High Risk subset.

## 10.3 Patient Demographics

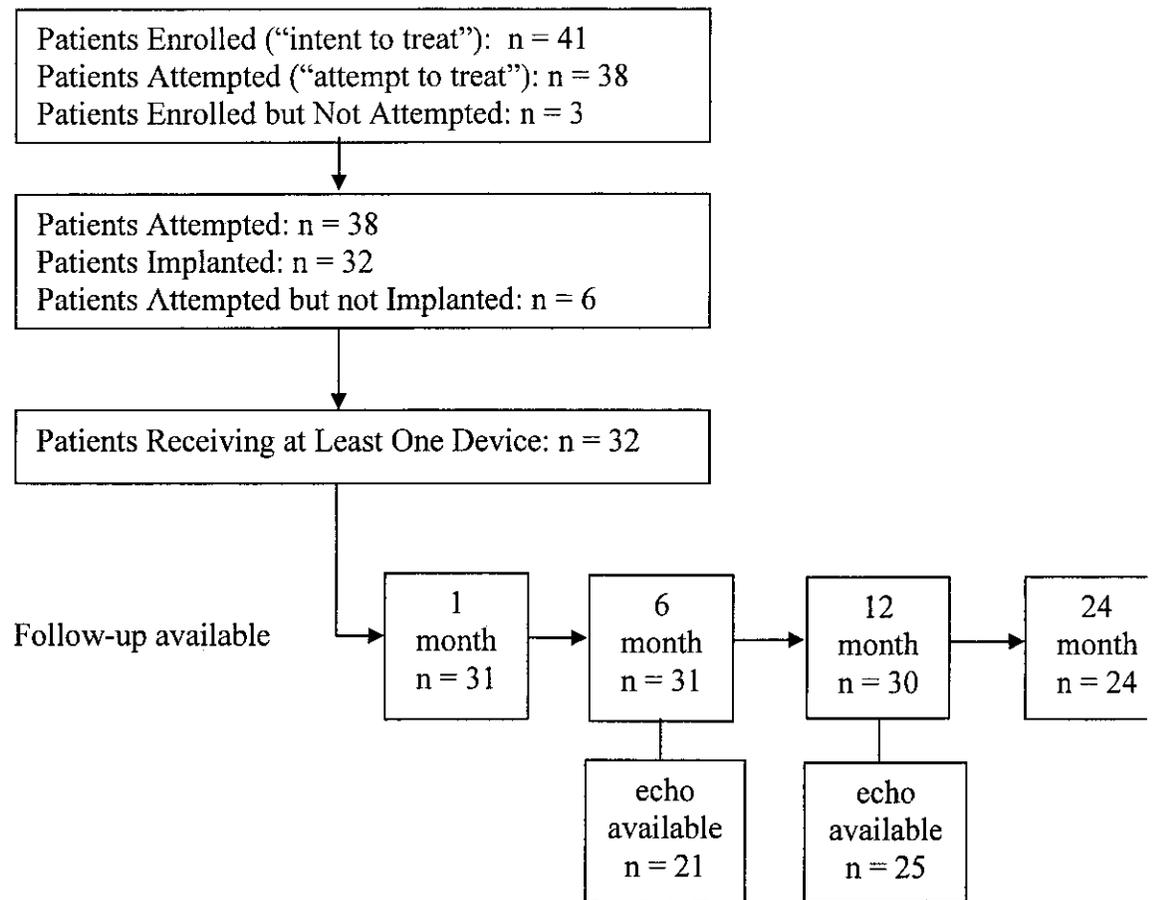
A total of 41 high risk patients were consented to participate in the clinical study and undergo transcatheter VSD closure with the AMPLATZER Muscular VSD Occluder. Of these 41 patients, 3 patients were classified as “intent to treat” patients in which the patient signed the informed consent but the patient was not exposed to the investigational device. The remaining 38 patients underwent a cardiac catheterization procedure and an attempt to place the AMPLATZER Muscular VSD Occluder. Six (6) of the 38 patients were “attempt to treat” patients in that a device was not successfully implanted during any procedure. The mean age of the 41 patients was 3.2 years (range 0.1 to 49.0 years) and 21 (55.2%) of the patients were male.

## 10.4 Study Protocol

Physical examinations and Doppler transthoracic echocardiograms (TTE) were performed pre-implant procedure and at follow-up. Clinical follow-up testing was required at hospital discharge, and at 1-month, 6-months, 12-months, and 24-months post-procedure. All reported adverse events were reviewed and adjudicated by an independent data safety monitoring board (DSMB). Adverse events were adjudicated according to severity (major, minor, observation), using definitions determined by the DSMB. Adverse event relationship to device and procedure, and whether the event was anticipated or not, was also determined by the DSMB. The ventricular septal defect(s) shunt status was evaluated at 1-month, 6-month, 12-month, and 24-month follow-up intervals using TTE and was classified according to degree: none, trivial (less than 1 mm), small (1 mm–2 mm), moderate (greater than 2 mm–4 mm) and large (greater than 4 mm). Of the 31 patients seen for the 6-month follow-up, an independent echo board reviewed tapes for 21 (67.7%) patients. Of the 30 patients who were seen at the 1-year follow-up visit, 25 (83.3%) patients had echo tapes reviewed by the board.

## 10.5 Principal Safety and Effectiveness Results

The following tables describe the principal safety and effectiveness results of the AMPLATZER Muscular VSD device in high risk patients. Of the 41 high risk patients enrolled in the study, there were three (3) “intent to treat” patients who signed the consent but were not exposed to the device. The remaining 38 patients underwent a cardiac catheterization during which device placement was attempted. Of these 38 patients, six (6) patients were “attempt-to-treat” patients meaning device placement was not successful at any time during the clinical trial. Two (2) additional patients had an “attempt to treat” procedure but at some point during the clinical trial also had a procedure with successful device placement. The following flow diagram depicts patients enrolled, patients who received at least one device and the number of patients who were seen at each follow-up interval.



The Acute Effectiveness table is broken down by patient, procedure, and finally by device. The data is also provided by patients attempted and also all consented patients.

Technical success by patient is defined as the number of patients who experienced only successful procedures, meaning that the patient did not have any procedures in which they left the catheterization lab without device placement. Acute procedure success by patient is defined as the number of patients who had a shunt less than or equal to 2 mm immediately post-procedure.

The second portion of the following table describes the results by procedure. Technical success by procedure was defined as the number of successful procedures. The acute procedure success was defined as procedures in which there was less than or equal to 2 mm residual shunt immediately post-procedure.

The last analysis was by device. Acute results by device were the number of devices successfully implanted. The acute procedure success closure results by device is the number of devices with a less than or equal to 2 mm residual shunt immediately post- procedure.

**Table 8: Acute Effectiveness**

Acute Results-Effectiveness	All Attempted Patients <sup>1</sup>	All Consented Patients <sup>2</sup>
<b>Acute Results by Patient</b>		
Technical Success <sup>3</sup>	30/38 (79.0%)	30/41 (73.2%)
Acute Procedure Success <sup>4</sup>	29/38 (76.3%)	29/41 (70.7%)
<b>Acute Results by Procedure</b>		
Technical Success <sup>5</sup>	39/47 (83.0%)	39/51 (76.5%)
Acute Procedure Success <sup>6</sup>	38/47 (80.9%)	38/51 (74.5%)
<b>Acute Results by device</b>		
Technical Success <sup>7</sup>	65/82 (79.3%)	--
Acute Procedure Success closure results <sup>8</sup>	64/82 (78.1%)	--

<sup>1</sup> Acute results for all attempted patients.

<sup>2</sup> Acute results for all consented patients.

<sup>3</sup> Number of patients who experienced only successful procedure(s), two of the eight technical-failure patients had both successful and unsuccessful procedure(s). Patients who did not receive the device are included in the denominator.

<sup>4</sup> Number of patients who had a shunt of less than or equal to 2 mm shunt immediately post-procedure

<sup>5</sup> Number of successful procedures.

<sup>6</sup> Number of procedures in which there was less than or equal to 2mm shunt immediately post-procedure

<sup>7</sup> Number of devices successfully implanted.

<sup>8</sup> Number of devices for which the shunt was less than or equal to 2mm shunt immediately post-procedure

Closure by follow-up period is reported both by Echo Board adjudication and by investigator. An independent Echo Board reviewed the 6-month and 12-month echocardiograms for a majority of the patients seen for each follow-up interval. They determined if there was residual shunting and if so, to what degree.

Closure is also reported as assessed by investigator for patients seen at the specific follow-up interval, for all attempted patients, and lastly for all

patients. Closure success is defined as patients who had a shunt of less than or equal to 2 mm at the specific follow-up interval.

**Table 9: Closure by Follow-up Period – Effectiveness**

Closure Success Defined as $\leq 2$ mm shunt at Follow-Up Interval		
Success by ECHO Board adjudication <sup>1</sup>	Results	95% Confidence Intervals <sup>7</sup>
Six-Month Success	20/21 (95.2%)	(76.2%; 99.9%)
Twelve-Month Success	25/25 (100.0%)	(86.3%; 100.0%)
Success by Investigator Assessment-Patients Seen <sup>2</sup>		
One-Month Success	30/31 (96.8%)	(83.3%; 99.9%)
Six-Month Success	29/31 (93.6%)	(78.6%; 99.2%)
Twelve-Month Success	28/30 (93.3%)	(77.9%; 99.2%)
24-Month Success	24/24 (100.0%)	(85.8%; 100.0%)
Success By Investigator Assessment-All Attempted Patients <sup>3, 4</sup>		
Acute Procedure Success	29/38 (76.3%)	(59.8%; 88.7%)
One-Month Success	30/38 (79.0%)	(62.7%; 90.5%)
Six-Month Success	29/38 (76.3%)	(59.8%; 88.6%)
Twelve-Month Success	28/38 (73.7%)	(56.9%; 86.6%)
24-Month Success	24/38 (63.2%)	(46.0%; 78.2%)
Success By Investigator Assessment -All Consented Patients <sup>5, 6</sup>		
Acute Procedure Success	29/41 (70.7%)	(54.5%; 83.9%)
One-Month Success	30/41 (73.2%)	(57.1%; 85.8%)
Six-Month Success	29/41 (70.7%)	(54.5%; 83.9%)
Twelve-Month Success	28/41 (68.3%)	(51.9%; 81.9%)
24-Month Success	24/41 (58.5%)	(42.1%; 73.7%)

<sup>1</sup> Number of patients who had their follow-up ECHO reviewed by the ECHO Board and had a shunt of less than or equal to 2 mm shunt at follow-up interval.

<sup>2</sup> Number of patients who were seen at follow-up interval, whether or not they had shunt evaluated, and had a shunt of less than or equal to 2 mm shunt at follow-up interval. Patients who were not seen but had a shunt greater than 2 mm at last follow-up interval are included in the denominator.

<sup>3</sup> Number of patients who had an attempted procedure and had a shunt of less than or equal to 2 mm shunt at follow-up interval.

<sup>4</sup> The six patients who did not have a device implanted are included in the denominator.

<sup>5</sup> Number of patients who had a shunt of less than or equal to 2 mm shunt at follow-up interval.

<sup>6</sup> The six patients who did not have a device implanted and the three patients who were never exposed to a device are included in the denominator (i.e., intent to treat).

<sup>7</sup> Confidence intervals are unadjusted for multiple comparisons.

In addition to Closure by Follow-up Period, a Composite Success parameter was calculated to comprehensively evaluate both the safety and effective performance of the device at the 1-month and 12-month follow-up intervals.

Composite Success was defined as patients in which device placement was attempted who did not experience technical failure, a major adverse event, or major shunt at the respective follow-up visit. Patients who were technical successes and did not have a major adverse event at the specific follow-up interval and did not have the shunt evaluated at the follow-up interval, but were classified as a failure at the shunt evaluation at their last follow-up interval, were classified as composite failures. Technical success patients

with no major adverse event at the specific follow-up interval who did not have the shunt evaluated at the follow-up interval, but were classified as a successful closure at the shunt evaluation at their last follow-up interval, were classified as missing.

**Table 10: Composite Results**

Composite Results		95% Confidence Intervals <sup>1</sup>
One-Month Composite Success	20/36 (55.6%)	(38.1%; 72.1%)
12-Month Composite Success	14/32 (43.8%)	(26.4%; 62.3%)

<sup>1</sup> Confidence intervals are unadjusted for multiple comparisons.

**Table 11: Major Adverse Events by Follow-up Period**

Major Adverse Events-Safety		
Major Adverse Event by Patient	Results <sup>1,2</sup>	95% confidence Interval <sup>3</sup>
Major AEs → at 24-Hour	16/39 (41.0%)	(25.6%; 57.9%)
Major AEs at → 1-Month	16/39 (41.0%)	(25.6%; 57.9%)
Major AEs at → 6-Months	17/39 (43.6%)	(27.8%; 60.4%)
Major AEs at → 12-Months	18/39 (46.2%)	(30.1%; 62.8%)
Major AEs at → 24-Months	18/39 (46.2%)	(30.1%; 62.8%)

<sup>1</sup> The numerator depicts the number of consented patients who experienced a major adverse event at the specific follow-up interval.

<sup>2</sup> The denominator includes the 38 attempted patients plus one “intent to treat” patient who experienced two major adverse events. The other two “intent to treat” patients did not experience a major adverse event and are not included in the denominator.

<sup>3</sup> Confidence intervals are unadjusted for multiple comparisons.

Mortality results are reported in multiple ways and a range of assumptions are made regarding the outcome of patients due to unavailable follow-up data. For example: death is reported with the assumption that for all consented patients, whether or not they were exposed to the device, who were not seen at a specific follow-up interval and never returned at a later date have died. This includes all “intent to treat” and “attempt to treat” patients who were discontinued immediately post procedure.

**Table 12: Mortality Results - Safety**

Mortality-Safety		
Mortality of all attempted patients <sup>1</sup>	Results	95% confidence Interval <sup>1</sup>
Mortality at → 24-Hours	0/38 (0.0%)	
Mortality at → 1-Month	1/38 (2.6%)	(0.1%; 13.8%)
Mortality at → 6-Months	1/38 (2.6%)	(0.1%; 13.8%)
Mortality at → 12-Months	2/38 (5.3%)	(0.6%; 50.8%)
Mortality at → 24-Months	2/38 (5.3%)	(0.6%; 50.8%)
Mortality of patients seen for follow-up <sup>2</sup>		
Mortality at → 24-Hours	0/33 (0.0%)	
Mortality at → 1-Month	1/33 (3.0%)	(0.1%; 15.8%)
Mortality at → 6-Months	1/32 (3.2%)	(0.1%; 16.2%)
Mortality at → 12-Months	2/32 (6.3%)	(0.8%; 20.8%)
Mortality at → 24-Months	2/28 (7.1%)	(0.9%; 23.5%)
Assumed Mortality of patients implanted with a device <sup>3,4</sup>		
Mortality at → 24-Hours	0/32 (0.0%)	
Mortality at → 1-Month	1/33 (3.0%)	(0.1%; 15.8%)

Mortality at → 6-Months	1/33 (3.0%)	(0.1%; 15.8%)
Mortality at → 12-Months	4/33 (12.1%)	(3.4%; 28.2%)
Mortality at → 24-Months	6/33 (18.2%)	(7.0%; 35.5%)
Assumed Mortality of all consented patients <sup>5,6</sup>	Results	95% confidence Interval <sup>7</sup>
Mortality at → 24-Hours	7/41 (17.1%)	(7.2%; 32.1%)
Mortality at → 1-Month	7/41 (17.1%)	(7.2%; 32.1%)
Mortality at → 6-Months	7/41 (17.1%)	(7.2%; 32.1%)
Mortality at → 12-Months	10/41 (24.4%)	(12.4%; 40.3%)
Mortality at → 24-Months	14/41 (34.2%)	(20.1%; 50.6%)

<sup>1</sup> Number of attempted patients with a known death at follow-up interval.

<sup>2</sup> Number of patients seen for follow-up at follow-up interval with a known death.

<sup>3</sup> Number of patients with at least one successful procedure who were discontinued for any reason at follow-up interval and patients with no successful procedures who have died.

<sup>4</sup> 12-month and 24-month intervals include the 2 patients who were discontinued due to death and additional patients who were discontinued for other reasons but are assumed to have died.

<sup>5</sup> Number of all consented patients who were not seen at the follow-up interval and never came back at a later date were assumed dead (i.e., intent to treat).

<sup>6</sup> One patient who died 3-weeks post-procedure was not evaluated at 24-hours post-procedure and is therefore assumed dead at the 24-hour follow-up interval.

<sup>7</sup> Confidence intervals are unadjusted for multiple comparisons.

**Table 13: Total Fluoroscopy Time Per-Patient**

Procedure variable	Results
Fluoro time (min) Mean +/- s.d. (N) [range]	95.5 +/- 93.7 (41) [8.7, 573.0]

**Table 14: Total Fluoroscopy Time Per-Procedure**

Procedure variable	Results
Fluoro time (min) Mean +/- s.d. (N) [range]	76.8 +/- 59.7 (51) [8.7, 356.0]

## 11. Gender Bias

The gender selection in the VSD study was based upon exclusion and inclusion criteria and male patients represented 53% of the population. The ratio of male to female patients in this investigation is reflective of the underlying distribution of the disease for the given age groups, ethnic groups and stages of disease in these populations. Limited patient sample size precluded an analysis of outcomes based on gender; however a qualitative analysis did not suggest a difference in outcomes for male versus female patients.

## 12. Conclusions Drawn From the Studies

Although no prospective hypothesis or statistical plan (including sample size) was developed for patients implanted with the VSD device, patients were followed prospectively for adverse events and shunt evaluation. Thirty-eight (38) patients underwent 47 procedures, 83% of the procedures were a technical success. Of the 6-month echocardiograms reviewed by an independent Echo Board, 95.2% of the patients had successful closure of the muscular VSD and 100% of the patients had successful closure at the 12-month follow-up visit. Additionally, 43.8% of patients

were classified as 12-Month Composite Successes in that they did not experience a major adverse event, technical failure or significant shunt within 12 months of the implant procedure.

Given the general health status of the patients in this high risk population, FDA finds these clinical outcomes to be supportive of device safety and effectiveness. It should be noted that patients who were amenable to safe surgical closure were excluded from the overall analysis because insufficient data were provided to establish reasonable assurance of safety and effectiveness of device closure compared to surgical closure in surgical candidates. Therefore, safety and effectiveness have been established only for those patients at high risk for surgical closure either due to anatomical cardiac or overall health conditions. The data provided supports safe and effective use of the Amplatzer device in this restricted patient population. Patients amenable to surgical closure were excluded from the overall analysis because the amount and quality of data collected were insufficient to support safety and effectiveness in this lower risk patient population. Furthermore, small patients (i.e., < 5.2 kgs) were observed to be at increased risk for adverse outcomes and were therefore contraindicated for device use, as were patients with post-infarction VSDs. In conclusion, the study data demonstrate a reasonable assurance of safety and effectiveness for the AMPLATZER Muscular VSD Occluder in High Risk patients with muscular VSD.

**13. *Panel Recommendation***

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Panel, and FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

**14. *CDRH Decision***

FDA issued an approval order on September 7, 2007. The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

**15. *Approval Specifications***

Direction for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precaution, and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.