The AMPLATZER® Septal Occluder System

Summary of Safety and Effectiveness Data

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1. General Information

Device Generic Name: Transcatheter Atrial Septal Defect Occlusion Device

Device Trade Name: AMPLATZER® Septal Occluder and
AMPLATZER® Delivery System

Applicant's Name and Address: AGA Medical Corporation
682 Mendelssohn Avenue
Golden Valley, MN 55427
USA

Date(s) of Panel Recommendation: September 10, 2001

Premarket Approval Application (PMA) Number: P000039

Date of Good Manufacturing Practice Inspection: October 2000

Date of Notice of Approval to Applicant:

2. Indications And Usage

The AMPLATZER® Septal Occluder (ASO) device is indicated for the occlusion of atrial septal defects (ASD) in secundum position. The ASO device is also indicated in patients who have undergone a fenestrated Fontan procedure and who now require closure of the fenestration.

Patients indicated for ASD closure have echocardiographic evidence of ostium secundum atrial septal defect and clinical evidence of right ventricular volume overload (i.e., 1.5:1 degree of left to right shunt or RV enlargement).

3. Contraindications

3.1 Any patient known to have extensive congenital cardiac anomaly which can only be adequately repaired by way of cardiac surgery.

3.2 Any patient known to have sepsis within one month prior to implantation, or any systemic infection that cannot be successfully treated prior to device placement.

3.3 Any patient known to have a bleeding disorder, untreated ulcer or any other contraindications to aspirin therapy, unless another anti-platelet agent can be administered for 6 months.

3.4 Any patient known to have a demonstrated intracardiac thrombi on echocardiography (especially left atrial or left atrial appendage thrombi).

3.5 Any patient whose size (i.e., too small for TEE probe, catheter size, etc) or condition (active infection, etc) would cause the patient to be a poor candidate for cardiac catheterization.

3.6 Any patient with the margins of the defect <5mm to the coronary sinus, AV valves or right upper lobe pulmonary vein.

4. Warnings and Precautions

The warnings and precautions can be found in the AMPLATZER Septal Occluder final labeling (Instructions for Use).

5. Device Description

The AMPLATZER® Septal Occluder is a self-expandable, double disc device made from a Nitinol wire mesh. The two discs are linked together by a short connecting waist corresponding to the size of the ASD. In order to increase its closing ability, the discs and the waist are filled with polyester fabric. The polyester fabric is securely sewn to each disc by a polyester thread.

Device Specifications

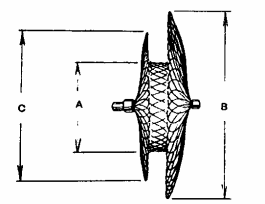

Table 1 - Device Specifications / Recommended sheath sizes

Order Number	A DEVICE SIZE (=STRETCHED ASD)	B LA DISC DIAMETER	WIDTH OF CONNECTING WAIST	C RA DISC DIAMETER	SMALLEST RECOMMENDED SHEATH SIZE
9-ASD-004	4 mm	16 mm	3 mm	12 mm	6-7 French
9-ASD-005	5 mm	17 mm	3 mm	13 mm	6-7 French
9-ASD-006	6 mm	18 mm	3 mm	14 mm	6-7 French
9-ASD-007	7 mm	19 mm	3 mm	15 mm	6-7 French
9-ASD-008	8 mm	20 mm	3 mm	16 mm	6-7 French
9-ASD-009	9 mm	21 mm	3 mm	17 mm	6-7 French
9-ASD-010	10 mm	22 mm	3 mm	18 mm	6-7 French
9-ASD-011	11 mm	25 mm	4 mm	21 mm	7 French
9-ASD-012	12 mm	26 mm	4 mm	22 mm	7 French
9-ASD-013	13 mm	27 mm	4 mm	23 mm	7 French
9-ASD-014	14 mm	28 mm	4 mm	24 mm	7 French
9-ASD-015	15 mm	29 mm	4 mm	25 mm	7 French
9-ASD-016	16 mm	30 mm	4 mm	26 mm	7 French
9-ASD-017	17 mm	31 mm	4 mm	27 mm	7 French
9-ASD-018	18 mm	32 mm	4 mm	28 mm	8-9 French
9-ASD-019	19 mm	33 mm	4 mm	29 mm	8-9 French
9-ASD-020	20 mm	34 mm	4 mm	30 mm	8-9 French
9-ASD-022	22 mm	36 mm	4 mm	32 mm	9 French
9-ASD-024	24 mm	38 mm	4 mm	34 mm	9 French
9-ASD-026	26 mm	40 mm	4 mm	36 mm	10 French
9-ASD-028	28 mm	42 mm	4 mm	38 mm	10 French
9-ASD-030	30 mm	44 mm	4 mm	40 mm	10 French
9-ASD-032	32 mm	46 mm	4 mm	42 mm	10 French
9-ASD-034	34 mm	50 mm	4 mm	44 mm	12 French
9-ASD-036	36 mm	52 mm	4 mm	46 mm	12 French
9-ASD-038	38 mm	54 mm	4 mm	48 mm	12 French

The AMPLATZER® Delivery System includes:

- **Delivery Sheath** with Touhy-Borst Adapter - used to deliver the device.
- **Dilator** – used to ease penetration of tissue.
- **Loading Device** – used to introduce the AMPLATZER Septal Occluder into the delivery sheath.
- **Plastic Vise** – facilitates directional control and serves as the "handle" for disconnecting (unscrewing) the delivery cable from the device.
- **Delivery Cable** – the device is screwed onto the distal tip of the delivery cable, which allows for placement (and if necessary, retrieval) of the device.

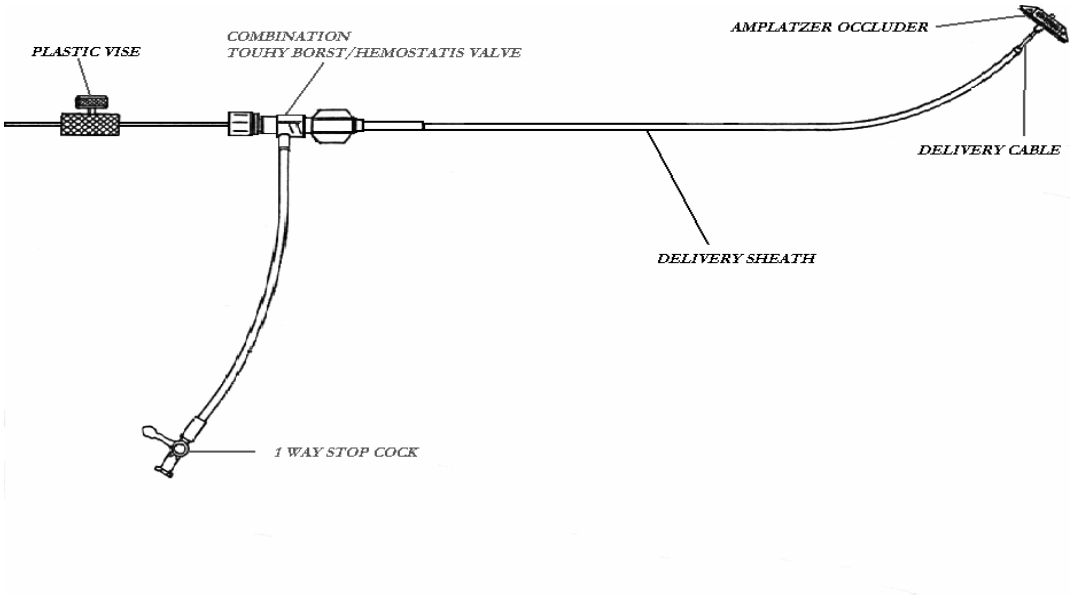

Figure 1 AMPLATZER Septal Occluder Device and Delivery System

6. Alternative Practices or Procedures

The only alternative to device closure of an ASD is open-heart surgery. Cardiac surgery that is required for closure of such defects is a major procedure that requires cardiopulmonary bypass. Surgery is relatively safe with a mortality of less than 1%. If the patient suffers from coexistent medical illnesses such as pulmonary disease, diabetes, renal failure, etc., the risks of surgery are higher.

7. Marketing History

These devices have not been marketed in the United States. The AMPLATZER Septal Occluder and Delivery System received the CE Mark in 1998. Additionally the AMPLATZER Septal Occluder and Delivery System has been marketed in the following countries:

Africa	India	Saudi Arabia
Argentina	Israel	Singapore
Australia	Italy	Slovakia
Austria	Jordan	Spain
Belgium	Korea	Sweden
Brazil	Kuwait	Switzerland
Canada	Lebanon	Taiwan
Chile	Malaysia	Thailand
China	Mexico	The Netherlands
Colombia	Monaco	Tunisia
Costa Rica	New Zealand	Turkey
Czech Republic	Norway	United Kingdom
Denmark	Pakistan	Uruguay
Finland	Poland	Venezuela
France	Portugal	
Germany	Russia	
Greece		
Hong Kong		

The AMPLATZER Septal Occluder has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device. The AMPLATZER Delivery Systems were voluntarily recalled by AGA Medical due to reports of dislodgment and embolization of the delivery sheath distal tip marker band. The sheaths are no longer manufactured with marker bands.

8. Adverse Events

8.1 Adverse Events of the Device on Health

The AMPLATZER Septal Occluder was evaluated in a multi-center, non-randomized, pivotal study comparing the device to surgical closure of atrial septal defects; 423 patients received 433 devices with a total device exposure of 911.5 years. Individual patient exposure to the device averaged 25.6 months (ranging from 0 to 38.9).

A Registry group was also studied to evaluate the device in patients with other conditions appropriate for device closure. Forty-eight (48) patients with Fenestrated Fontan (FF) (communication in the baffle with at least 5mm distance from the free atrial wall and central venous pressure less than 15Hg) were enrolled in the study.

There was one death reported in the pivotal study (device group) and no deaths were reported in the Fenestrated Fontan Registry Group. The Data Safety Monitoring Board determined that the death was not device or procedure related.

Table 1 Adverse Events – Pivotal Study

Major Adverse Events	AMPLATZER Patients	Surgical Control Patients	p-value
Cardiac Arrhythmia requiring major treatment	2/442 (0.5%)	0/154 (0.0%)	1.00
Device Embolization with surgical removal	3/442 (0.7%)	0/154 (0.0%)	0.57
Device Embolization with percutaneous removal	1/442 (0.2%)	0/154 (0.0%)	1.00
Delivery System Failure	1/442 (0.2%)	0/154 (0.0%)	1.00
Pericardial Effusion with tamponade	0/442 (0.0%)	3/154 (1.9%)	0.017
Pulmonary Edema	0/442 (0.0%)	1/154 (0.6%)	0.26
Repeat Surgery	0/442 (0.0%)	2/154 (1.3%)	0.066
Surgical Wound Adverse Event	0/442 (0.0%)	2/154 (1.3%)	0.066
Total Major Adverse Events Patients	7/442 (1.6%)	8/154 (5.2%)	0.030

Table 1 Adverse Events – Pivotal Study (continued)

Minor Adverse Events	AMPLATZER Patients	Surgical Control Patients	p-value
Anemia	0/442 (0.0%)	1/154 (0.6%)	0.26
Allergic reaction (drug)	2/442 (0.5%)	0/154 (0.0%)	1.00
Atelectasis	0/442 (0.0%)	1/154 (0.6%)	0.26
Cardiac Arrhythmias Minor Treatment	15/442 (3.4%)	9/154 (5.8%)	0.23
Device Embolization with percutaneous removal	1/442 (0.2%)	0/154 (0.0%)	1.00
Extremity Tingling/Numbness	1/442 (0.2%)	0/154 (0.0%)	1.00
Headaches/Possible TIA	2/442 (0.5%)	0/154 (0.0%)	1.00
Delivery System Failure	2/442 (0.5%)	0/154 (0.0%)	1.00
Pericardiotomy Syndrome	0/442 (0.0%)	2/154 (1.3%)	0.066
Pericardial effusion	0/442 (0.0%	6/154 (3.9%)	<0.001
Pleural Effusion	0/442 (0.0%)	1/154 (0.6%)	0.26
Pneumothorax	0/442 (0.0%)	3/154 (1.9%)	0.017
Staph Infection	0/442 (0.0%)	1/154 (0.6%)	0.26
Surgical Wound Adverse Events	0/442 (0.0%)	1/154 (0.6%)	0.26
Thrombus formation	3/442 (0.7%)	0/154 (0.0%)	0.56
Transfusions	0/442 (0.0%)	2/154 (1.3%)	0.066
Upper Respiratory Infection/Fever	0/442 (0.0%)	2/154 (1.3%)	0.066
Urinary Tract Disturbance	1/424 (0.2%)	0/154 (0.0%)	1.00
Total Minor Adverse Events (Patients)	27/442 (6.1%)	29/154 (18.8%)	<0.001

Table 2: Adverse Events -FF

	AMPLATZER Patients	Upper 95% Confidence Bound
Major Adverse Events		
Repeat Surgery	1/48 (2.1%)	0.095
Hemothorax	1/48(2.1%)	0.095
Minor Adverse Events		
Vomiting (required 2 nights in hospital)	1/48 (2.1%)	0.095
Atrial fibrillation/cardioversion	1/48 (2.1%)	0.095
Total Adverse Events	4/48 (8.3%)	0.181

8.2 Potential Adverse Events

Placement of the AMPLATZER Septal Occluder involves using standard interventional cardiac catheterization techniques. The following adverse events (listed in alphabetical order) might be expected from interventional cardiac catheterization techniques.

- Air embolus
- Allergic dye reaction
- Anesthesia reactions
- Apnea
- Fever

- Hypertension/hypotension
- Infection including endocarditis
- Perforation of vessel or myocardium
- Pseudoaneurysm including blood loss requiring transfusion
- Valvular regurgitation

9. Summary Of Preclinical Studies

9.1 Bench Testing

Bench testing was done to ensure that all initial design requirements were met. Bench testing has demonstrated the strength and reliability of the device. Design verification of the device and its components has been conducted to verify that the device is safe for its intended use.

Table 3 Summary of AMPLATZER Septal Occluder Testing

Test	Samples		Specification	Results			
Pull Test Laser Weld – Marker Bands to Wire Braid	**Wire Dia.**	**N**	.004 - .006" diameter wire >12 lbs .007" diameter wire >24 lbs .008" diameter wire > 32.2 lbs	**Wire diameter**	**Mean ± SD (range) lbs**		
	.004"	9		.004"	30.3 ± 2.6 (26.3-35.5)		
	.005"	10		.005"	36.79 ± 3.3 (32.9 – 40)		
	.006"	11		.006"	37.6 ± 3.8 (29.9 – 42.6)		
	.007"	5		.007"	49.8 ± 6.2 (41.2 - >55)		
	.008"	5		.008"	All samples exceeded 55 lbs		
Pull Test Laser Weld-Screw Attachment to Marker Bands	**Wire Dia.**	**N**	.004 - .006" diameter wire >12 lbs .007" diameter wire >24 lbs .008" diameter wire > 32.2 lbs	**Wire Diameter**	**Mean ± SD (range) lbs**		
	.004"	5		.004"	34.8 ± 7.6 (28.3-45.3)		
	.005"	7		.005"	38.3 ± 5.8 (31.1 – 47)		
	.006"	10		.006"	47.9 ± 4.9 (34.95 – >50)		
	.007"	5		.007"	49.8 ± 6.2 (41.2 - >55)		
	.008"	5		.008"	All samples exceeded 55 lbs		
Pull Test Delivery Cable screw and device end screw	5		12 lbs	**Mean ± SD (range) lbs** 26.4 ± 2.3 (23.4 – 29.15)			
Device Integrity	1		Structural Integrity must remain intact.	Structural integrity remained intact when single and multiple wires were cut, as well as when the left atrial disc post was cut.			
Life Cycle	300 (30 each of the smallest & largest device in each of the wire diameters)		Structural integrity must remain intact after 400 million cycles	Size	Wire dia.	# Fail	Description of findings
				4	.004"	0	
				10	.004"	0	
				11	.005"	0	
				17	.005"	2[1]	1) 1 broken wire near end screw 2) 1 broken wire near marker band
				18	.006"	0	
				24	.006"	1	Broken wires in waist. Brass metal shaving found sandwiched between the two device discs during removal
				26	.007"	0	
				34	.007"[2]	0	
				34	.008"	0	
				40	.008"	0	

[1] In both cases, the devices had retained their preset shape and had to be compressed several times to detect the broken wires. If a wire were to fracture in the clinical setting, it would not protrude due to the shape memory property of Nitinol.

[2] Initially, the 34mm device was manufactured with .007" wire. It was later changed to .008" wire.

Table 4 Summary of AMPLATZER Delivery System Testing

Test	Samples		Specification	Results	
Delivery Sheath Kink Resistance	**Size**	**N**	The sheath must not kink during normal clinical use.	**Size**	**Mean ± SD (range) degrees**
	6F	4		6F	131.3 ± 4.8 (125 – 135)
	7F	4		7F	118.8 ± 2.5 (115 – 120)
	8F	4		8F	112.5 ± 6.5 (105 – 120)
	9F	4		9F	112.5 ± 2.9 (110 – 115)
	10F	5		10F	106 ± 5.5 (100 – 110)
	12F	5		12F	129 ± 4.2 (125 – 135)
Delivery Cable Kink Resistance	10		The cable must not kink during normal clinical use.	**Mean ± SD (range) degrees** 128.5 ± 7.8 (120-145)	
Pull Tests - Delivery Sheath Hub to Tubing	**Size**	**N**	Pull strength must not be <3lbs.	**Size**	**Mean ± SD (range) lbs**
	6F	4		6F	8 ± 1.3 (6.85 – 9.25)
	7F	4		7F	10.5 ± 0.1 (10.3 – 10.7)
	8F	4		8F	11.3 ± 0.1 (11.3 – 11.5)
	9F	4		9F	11.6 ± 0.1 (11.5 – 11.8)
	10F	5		10F	14.3 ± 0.1 (14.2 – 14.4)
	12F	5		12F	17.3 ± 1.0 (16.2 – 18.7)
Pull Test – Delivery Cable – Cable to Cable Screw Weld Joint	10		12 pounds	**Mean ± SD (range) lbs** 46.1 ± 5.5 (37 - >50)	

9.2 MRI Compatibility

Two AMPLATZER Septal Occluders were placed in a water phantom, fixed with adhesive tape, and examined by a Siemens 1.5 Tesla MRI apparatus. Various imaging modalities were used and minimal artifacts were only observed in the object vicinity. The device is MRI safe up to 1.5 Tesla.

9.3 Corrosion Testing

9.3.1 Corrosion – Bench Testing

The device was tested per ASTM F746. The Nitinol sample did not display the general pitting found on the 316SS sample. In addition, there was no indication of crevice corrosion on the nickel-titanium sample as was seen on the 316 SS samples.

Eight devices were tested for corrosion potential. The devices were degreased, rinsed with deionized water and blown with dry air. The electrolyte was prepared by dissolving 36.9g reagent grade sodium chloride in deionized water. After transfer to the corrosion cell, the electrolyte was deoxygenated by sparging with zero grade nitrogen for a minimum of 60 minutes.

The devices were suspended in the corrosion cell and maintained in the electrolyte at open circuit for 60 minutes before beginning the polarization

scan (0.6 V/h). The electrochemistry was performed with a PAR 263 Potentiosatat.

In all devices the onset of corrosion occurred ca. 0.08 V from the open circuit potential. The corrosion potential (E_{CORR}) for the samples tested varied by ca. 0.08 V. The shape of the hysteresis curve indicates that localized corrosion may occur.

9.3.2 Corrosion – Animal Testing

Post mortem examination was conducted in an animal specimen wherein two devices were implanted (device #1 – implanted 18 months and device #2 implanted 14 months). Although the animal was implanted with the AMPLATZER Muscular Ventricular Septal Occluder device, materials and methods are identical to the AMPLATZER Septal Occluder.

Analysis revealed both devices were nearly covered by neoendocardium. Gross inspection revealed no wire breakage. Light microscopy at 40x revealed a smooth surface. Scanning electron microscopy was carried out and compared to a new control wire. Both surfaces appear identical. The wire surface appearance was typical of oxidized Nitinol wire.

Both devices were weighed (275 mg and 156 mg). No evidence of corrosion was observed for either device.

9.3.3 Abrasion

A device was explanted from a swine after 3 months (at least 26 million cycles). A biopsy was taken from the neo-endocardium for histologic examination. The device was examined grossly, by light microscopy and by scanning electron microscopy (SEM). No broken wires were detected.

SEM examination was made at randomly selected wire intersection on both the large and small discs. The typical condition of the wires at the intersections was photographed. Results indicate that there are no signs of intersecting wires abrading each other.

9.4 Biocompatibility Tests

The AMPLATZER Septal Occluder is constructed of Nitinol (a nickel-titanium alloy) and polyester. Sufficient information from the literature exists to demonstrate biocompatibility of the Nitinol for use in an implantable device.[3,4,5].

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[3] Castleman LS, Motzkin SM, Alicandri FP, et al. Biocompatibility of Nitinol Alloy as an Implant Material. *J of Biomedical Materials Research* 1976; 10:695-731.

[4] Cragg AH, De Jong SC, Barnhardt WH, et al: Nitinol Intravascular Stent: Results of Preclinical Evaluation. *Radiology* 1993; 189-775.

The polyester fabric and the patient contacting components of the delivery system underwent biocompatibility testing in accordance with FDA General Program Memorandum G95-1, which provides an FDA-modified matrix of International Standard ISO 10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing."

Table 5 – Summary of Biocompatibility Testing

Test	***Result***	
	Polyester Fabric	***Delivery System***
Cytotoxicity	Pass	Pass
Sensitization	Non-sensitizer	Non-sensitizer
Hemolysis	Non hemolytic	Non-hemolytic
Intracutaneous Injection (Irritation)	Pass	Pass
Toxicity	Pass (Subchronic)	Pass (Systemic)
Acute Systemic Injection	Pass	*Not required*
Ames Salmonella Mutagenicity	No mutagenic activity	*Not required*
Implantation	Moderate reaction*	*Not required*
Chronic Toxicity	Pass	*Not required*

*A "moderate reaction" is exactly what is expected when tissue ingrowth is the desired result.

9.5 Useful Life (Sterilization/Shelf Life)

The AMPLATZER Septal Occluder and Delivery System are single-use devices which are provided sterile (via ethylene oxide) to the user. The sterilization cycle was validated to ensure successful sterilization to a Sterility Assurance Level (SAL) of 10^{-6} .

Product and package stability testing of the AMPLATZER Septal Occluder and Delivery System was performed. Visual inspection and physical testing indicated that the device performed within product specification for up to 3 years. Based upon these results, an expiration date of 3 years has been established.

9.6 Animal Testing

Animal studies were conducted to evaluate the device design and to demonstrate that the AMPLATZER Septal Occluder was capable of providing rapid closure and endothelialization of atrial septal defects without evidence of residual shunting. Twelve (12) Yucatan minipigs underwent surgical creation of an atrial septal defect and were allowed to recover for 10 – 14 days. The animals were then implanted with the AMPLATZER Septal Occluder.

Sequential angiographic studies and blood gas measurements were repeated at one week, one month and three month intervals. The animals were then euthanized with removal of the heart and lungs for gross and histologic examination.

[5] Prince MR, Salzman EW, Schoen, FJ, et al: Local Intravascular Effects of the Nitinol Blood Clot Filter. *Investigative Radiology* 1998; 23:294-300.

At 3 months all animals studied exhibited complete endothelialization by neoendothelium. This tissue in-growth demonstrated that the device was firmly fixed into position and was covered by a glistening non-thrombogenic layer of cells. In this final state, it was apparent that no thrombosis, shunting or dislodgment occurred.

10. Summary Of Clinical Studies

10.1 Objective

The objective of the study was to compare the clinical performance of the AMPLATZER Septal Occluder device for atrial septal defect (ASD) closure with that documented for the ASD Surgical Repair Procedure. A Registry Group was also studied to evaluate the device in patients with Fenestrated Fontan.

10.2 Study Design

A multi-center, non-randomized, controlled clinical study was performed to evaluate the safety (incidence of major adverse events) and effectiveness (closure of the defect defined as $\leq$ 2mm shunt) of the AMPLATZER Septal Occluder.

Pivotal Study

Enrolled patients had echocardiographic evidence of ostium secundum atrial septal defect (device group: defect size $\leq$ 38mm) and clinical evidence of right ventricular volume overload or had clinical symptoms such as paradoxical embolism or atrial dysrhythmia in the presence of a minimal shunt. Exclusion criteria included:

- Patients with multiple defects that could not be adequately covered by the device (device group only).
- Associated congenital cardiac anomalies requiring surgery.
- Ostium primum or sinus venosus atrial septal defects.
- Partial anomalous pulmonary venous drainage.
- Pulmonary vascular resistance above 7 Woods units or a right-to-left shunt at the atrial level with a peripheral arterial saturation < 94%.
- Patients with recent myocardial infarction, unstable angina and decompensated congestive heart failure.
- Patient with right and/or left ventricular decompensation with ejection fraction < 30%.
- Sepsis.
- History of repeated pulmonary infection.
- Any type of serious infection < 1 month prior to procedure.
- Malignancy where life expectancy was < 2 years.
- Demonstrated intracardiac thrombi on echocardiography.
- Weight < 8 Kilograms.
- Inability to obtain informed consent.

- Patients with gastritis, gastric ulcer, duodenal ulcer, bleeding disorders etc. and other contraindications to aspirin therapy unless other anti-platelet agents can be administered for 6 months.

Registry Group

The inclusion criteria for the Registry group were:

- **Fenestrated Fontan** (communication in the baffle with at least 5mm distance from the free atrial wall and central venous pressure less than 15Hg).

10.3 Patient Description and Accountability

Patients were enrolled into the pivotal study from March 1998 through March 2000 at 29 centers in the United States. Device placement was attempted in 442 patients. In 18 patients the device was recaptured prior to releasing from the delivery cable due to anatomical conditions. There was one acute embolization. Thus 423 patients received 433 devices. ASD surgical data was collected prospectively in 117 patients and retrospectively in 37 patients.

Table 6: Patient Baseline Demographics

Variable	AMPLATZER Patients	Surgical Control Patients	p-value
Age (years) Mean±s.d.(N) [range]	18.1 ± 19.3 (442) [0.6, 82.0]	5.9 ± 6.2 (154) [0.6, 38.2]	<0.001
Gender			
Female	299/442 (67.6%)	94/154 (61.0%)	0.14
Male	143/442 (32.4%)	60/154 (39.0%)	
Height (cm) Mean±s.d.(N) [range]	134.6 ± 32.0 (440) [58,188]	105.5 ± 26.9 (151) [60,178]	<0.001
Weight (kg) Mean±s.d (N) [range]	42.3 ±27.3 (440) [6.3,130]	20.6 ± 15.2 (153) [4.8,78.4]	<0.001
Medical History			
CHF	11/442 (2.5%)	7/154 (4.5%)	0.27
Failure to Thrive	14/442 (3.2%)	13/154 (8.4%)	0.012
CAD	9/442 (2.0%)	0/154 (0%)	0.12
Respiratory Infections	7/442 (1.6%)	13/154 (8.4%)	<0.001
TIA	6/442 (1.4%)	1/154 (0.6%)	0.68
COPD	1/442 (0.2%)	0/154 (0%)	1.00
Hypertension	16/442 (3.6%)	0/154 (0%)	0.016
Stroke	13/442 (2.9%)	0/154 (0%)	0.026
Recurrent Strokes/TIA's	5/442 (1.1%)	1/154 (0.6%)	1.00
Diabetes	4/442 (0.9%)	0/154 (0%)	0.58

Table 7: Pre-Closure –Fenestrated Fontan

Age (years)	Mean±s.d (N) [range]	7.8 ± 6.9 (48) [1.6, 44.9]
Gender: Female		29/48 (60.4%)
Height (cm)	Mean±s.d.(N) [range]	114.5 ± 25.2 (46) [78,168]
Weight (kg)	Mean±s.d (N) [range]	22.4 ± 13.5 (48) [9.7, 68.7]
Medical History:		
CHF		1/48 (2.1%)
Failure to thrive		1/48 (2.1%)
Stroke		2/48 (4.2%)
Heart Murmur		26/47 (55.3%)
Pulmonary Ejection Murmur		2/47 (4.3%)
Mid Diastolic Murmur		1/47 (2.1%)
Right axis deviation		11/45 (24.4%)
Peaked p waves		1/45 (2.2%)
Cardiomegaly		20/45 (44.4%)

11. Data Analysis and Results

Patients with ostium secundum atrial septal defects and clinical evidence of right ventricular volume overload who were being evaluated for ASD closure underwent physical examination which included: heart murmur classification; an electrocardiogram (EKG) to document cardiac electrical characteristics; a chest x-ray to evaluate heart size and pulmonary vasculature; a detailed 2D Color Doppler Transthoracic Echo (TTE) to evaluate the atrial septal defect location, number of ASD's, size of the ASD's, and distance from the ASD to the coronary sinus, pulmonary vein, and AV valves.

The patients were instructed to avoid strenuous activity for a period of one month. and to take aspirin for 6 months post placement (3-5mg/kg/day). Additionally, patients were examined and a transthoracic Echocardiogram (TTE) was conducted at 24 hours, 6 months and 1 year. Post-discharge data was collected in surgical patients when available. Ninety-four (94) surgical repair patients were confirmed to be closed by echo at 12 months. All were assumed closed at 12 months. Trivial and small shunts were considered hemodynamically insignificant.

An independent core lab assessed a subset of echo videotapes for 12-month shunt status; a Data Safety Monitoring Board adjudicated all adverse events.

Table 8: Principal Effectiveness and Safety Results - Pivotal Study

	AMPLATZER Patients[1]	Surgical Control Patients	90% Confidence Interval
Technical Success	423/442 (95.7%)	154/154 (100.0%)	(-0.084,-0.010)
Procedure Success	413/423 (97.6%)	154/154 (100.0%)	(-0.059, +0.008)
Early (≤ 30 days) Composite Success	401/442 (90.7%)	148/154 (96.1%)	(-0.111, -0.005)
12-month Composite Success	331/362 (91.4%)	146/154 (94.8%)	(-0.096, +0.019)
24-hour Closure Success	404/418 (96.7%)	154/154 (100%)	(-0.073, -0.001)
6-month Closure Success	376/387 (97.2%)	154/154 (100%)	(-0.068, +0.003)
12-month Closure Success	326/331 (98.5%)	149/149 (100%)	(-1.052, 0.017)
Principal Safety Measures			
Major Adverse Events 12-months	7/442 (1.6%)	8/154 (5.2%)	(-0.090, -0.002)
Minor Adverse Events 12-months	27/442 (6.1%)	29/154 (18.8%)	(-0.200, -0.070)
12-month Composite Success (K-M)	0.934	0.938	[-0.077, +0.036]
Survival at 30 days (K-M)	0.939	0.956	[-0.052, +0.018]
Survival at 180 days (K-M)	0.936	0.947	[-0.048, +0.026]

Table 9: Principal Effectiveness and Safety Results - Pivotal Study
Patient Age < 20 years

	AMPLATZER Patients	Surgical Control Patients	90% Confidence Interval
Technical Success	315/328 (96.0%)	149/149 (100%)	(-0.086, -0.005)
Procedure Success	306/315 (97.1%)	149/149 (100%)	(0.074, +0.005)
Early (≤ 30 days) Composite Success	295/328 (89.9%)	143/149 (95.9%)	(-0.124, -0.007)
12-month Composite Success	256/281 (91.1%)	142/149 (95.3%)	(-0.108, +0.013)
24-hour Closure Success	301/310 (97.1%)	149/149 (100%)	(-0.075, +0.005)
6-month Closure Success	270/278 (97.1%)	149/149 (100%)	(-0.077, +0.006)
12-month Closure Success	246/251 (98.0%)	149/149 (100%)	(-0.068, +0.014)
Principal Safety Measures			
Major Adverse Events 12-months	6/328 (1.8%)	7/149 (4.7%)	(-0.086, +0.008)
Minor Adverse Events 12-months	16/328 (4.9%)	29/149 (19.5%)	(-0.221, -0.085)
12-month Composite Success (K-M)	0.930	0.944	[-0.055, +0.027]
Survival at 30 days (K-M)	0.933	0.954	[-0.059, +0.017]
Survival at 180 days (K-M)	0.930	0.954	[-0.062, +0.014]

[1]Unit of analysis = Patient. Although 10 patients had 2 defects each treated with an AMPLATZER Septal Occluder; all patients with multiple AMPLATZER implants were successfully treated.

Technical Success: successful deployment of the device, or the successful completion of the surgical procedure.

Procedure Success: successful closure of the defect as measured immediately following the procedure (≤ 2 mm residual shunt)

Composite Success: All device placement attempts without a major adverse event, surgical reintervention, embolization, technical failure or major shunt (defined as > 2 mm).

Closure Success: among patients that were technical successes, closure of the atrial septal defect (defined as a shunt ≤ 2mm) without the need for surgical repair.

Major Adverse Events: Events that are life threatening, prolong hospitalization or have long-term consequences or need for ongoing therapy. These include but are not limited to cerebral embolism, cardiac perforation with tamponade, endocarditis, pericardial effusion with tamponade, repeat surgery, death, cardiac arrhythmias requiring permanent pacemaker placement or long term anti-arrhythmic medication and device embolizations requiring immediate surgical removal.

Minor Adverse Events: Device embolization with percutaneous retrieval, cardiac arrhythmia with treatment, phrenic nerve injury, hematoma, other vascular access site adverse events, retroperitoneal hematoma, surgical wound adverse events, other procedural adverse events, pericardial effusion requiring medical management, evidence of device associated thrombus formation without embolization (with or without treatment) and marker band embolization without known sequelae.

Table 9: Principal Efficacy Results—FF

PRINCIPAL EFFECTIVENESS RESULTS	AMPLATZER Patients	Lower 95% Confidence Bound
Technical Success	46/48 (95.8%)	0.875
Procedure Success	46/46 (100.0%)	0.937
Early Composite Success	44/48 (91.7%)	0.819
6 month Success	38/38 (100.0%)	0.924
Primary Efficacy Outcome (12 month Success)	32/32 (100.0%)	0.911
Hospital days Mean±s.d. (N) [range]	1.2± 0.7 (39) [0.0, 4.0]	(0.95, 1.41)

Table 10: Principal Safety Results – FF

PRINCIPAL EFFECTIVENESS RESULTS	AMPLATZER Patients[1]	Upper 95% Confidence Bound
Major Adverse Events	2/48 (4.2%)	0.125
Minor Adverse Events	2/48 (4.2%)	0.125
Total Adverse Events	4/48 (8.3%)	0.181

[1]Unit of analysis = patient

12. Device Failures and Replacements

Device: Reported device failures include deformed upon deployment ("cobra") and immediate device embolization

Delivery System: Marker band embolization, sheath kink/accordion, and leaking hubs have been reported for the delivery system.

13. Conclusions Drawn From The Studies

13.1 Atrial Septal Defects

Effectiveness of the AMPLATZER Septal Occluder for treatment of atrial septal defects has been demonstrated by:

- Successful closure of ASD's at 12-month follow-up without the need for additional surgical repair in 326 out of 331 patients.
- These results are statistically equivalent to the 100% rate reported for the ASD Surgical Repair Control group. The Lower 95% confidence bound for the difference in 12-month success rate is -1.052, which is greater than the protocol specified requirement of -.08.
- The adverse event rates associated with the use of the AMPLATZER device at 12 months are within the protocol-defined acceptable limits. The mortality rate for the device cohort was 0%, which is less than the proposed 2%; the major adverse event rate for AMPLATZER patients was 1.6%, which is less than the proposed 10% rate. The overall AMPLATZER adverse event rate (7.2%) was statistically significantly lower than that reported for the control group (24.0%) ($p = <0.001$).
- In addition to a high rate of effectiveness and a low risk of major adverse events, the mean length of hospital stay for AMPLATZER patients of 1 day is statistically significantly lower than the mean of 3.4 days documented for the ASD Surgical Repair control group ($p <0.001$).

13.2 Fenestrated Fontan

Effectiveness of the AMPLATZER Septal Occluder for treatment of Fenestrated Fontans has been demonstrated by:

- Results consistent with those obtained for treatment of ASD.
- Primary Efficacy Outcome at 12 months follow-up without the need for additional surgical repair in 32 of 32 patients, obviates the need for a second surgical procedure in this patient population.
- The adverse event rates associated with the use of the AMPLATZER device at 12 months are within the protocol-defined acceptable limits. The mortality rate for the device cohort was 0%, which is less than the proposed 2%; the major adverse event rate for AMPLATZER patients was 4.2%, which is less than the proposed 10% rate.

In conclusion, the AMPLATZER® device operates as designed and is safe and effective in the clinical environment in the intended patient population and is appropriate for market release.

14. Panel Recommendation

At an advisory meeting held on September 10, 2001, the Circulatory System Devices recommended that Amplatzer® ASO System be approved subject to the submission to, and approval by, the Center for Devices and Radiological Health (CDRH) the following:

- changes to the labeling for the Amplatzer® ASO System;
- items to be incorporated into the training program; and
- collection of 5-year follow-up data for patients enrolled in the clinical investigations contained in the PMA.

15. CDRH Decision

CDRH concurred with the Circulatory System Devices Panel recommendation of September 10, 2001, and conveyed the Conditions of Approval in a facsimile dated November 11, 2001. AGA Medical indicated concurrence with those Conditions of Approval.

FDA issued an approval order on _____. The applicant's manufacturing facility was inspected on October 30, 2000 and contract sterilization facility was inspected on May 1, 2001. These facilities were found to be in compliance with the device Good Manufacturing Practice regulations.

16. Approval Specifications

Indications for Use: See the Instructions for Use (Attachment 1)

Hazards to Health from use of the Device: See CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, and ADVERSE EVENTS in the Instructions for Use (Attachment 1).

Postapproval requirements and restrictions: See approval order.

The Approval Order, Summary of Safety and Effectiveness Data, and labeling can be found on the Internet at address _____.