SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Replacement Heart Valve

Device Trade Name: ATS 3f® Aortic Bioprosthesis, Model 1000 (sizes 21, 23, 25, 27, and 29mm)

Applicant's Name and Address: ATS Medical, Inc.
20412 James Bay Circle
Lake Forest, CA 92630

Date of Panel Recommendation: none

Premarket Approval Application (PMA) Number: P060025

Date of FDA Notice of Approval: October 30, 2008

Expedited: not applicable

II. INDICATIONS FOR USE

The ATS 3f® Aortic Bioprosthesis, Model 1000 is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves.

III. CONTRAINDICATIONS

The ATS 3f® Aortic Bioprosthesis, Model 1000 should not be used in those patients who present with congenital bicuspid anatomy or other forms of abnormal aortic root geometry.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ATS 3f Aortic Bioprosthesis labeling.

V. DEVICE DESCRIPTION

The ATS 3f® Aortic Bioprosthesis, Model 1000 (Model 1000) is a stentless pericardial aortic heart valve replacement designed as a tubular structure and constructed from three equal sections of equine pericardium. The proximal orifice of the valve has an attached thin polyester sewing ring used to attach the bioprosthesis to the aortic root orifice after resection of the diseased aortic valve. The distal portion of the valve has three commissural tabs, formed from contiguous sections of each of the leaflets and reinforcing polyester material that are used to attach the commissures to the native aortic wall. The device is provided sterile in sterilant solution.

Accessories

Obturators - Obturators for each size valve are available for use with the ATS 3f® Aortic Bioprosthesis, Model 1000. The sizing obturators are designed to permit direct confirmation of their fit within the annulus.

Disposable Valve Holder Assembly and Reusable Handle - The disposable valve holder attached to the valve consists of two parts:
1) the outer holder which is attached to the inflow of the valve, and
2) the inner holder which is attached to the outflow tabs of the valve

A reusable handle is provided and attaches to the disposable valve holder to aid in valve removal from the container and valve implantation.

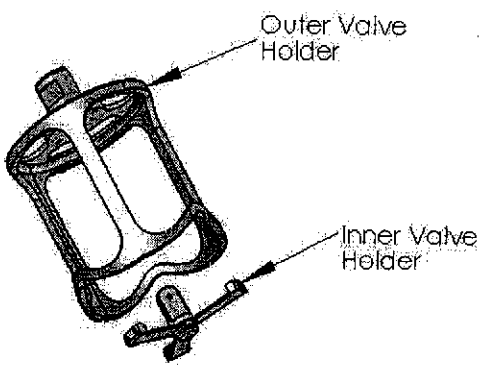

Figure 10

Steam Sterilization of Reusable Handles and Obturators - Reusable handles and obturators are supplied non-sterile and must be cleaned and sterilized before each use.

The following conditions are recommended:

Autoclave Cycle:
132°C [270°F] for 30 minutes

Each institution should employ procedures that include biological indicators to determine the effectiveness of the sterilization procedure.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of diseased, damaged or malfunctioning native or prosthetic aortic heart valve: allografts, other commercially available prosthetic heart valves and cardiac drug therapy. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Commercial distribution of the Model 1000 outside the U.S. began in October 2004. Currently, the device is approved for distribution in the 27 member states under the European Union, Canada, New Zealand, Norway, Saudi Arabia, Switzerland and Turkey. The Model 1000 has not been withdrawn from the market in any country for any reason related to the safety and effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Leak (transvalvular, perivalvular)
- Cardiac Dysrhythmias
- Endocarditis
- Hemolysis
  Hemorrhage
- Non-Structural Dysfunction [NSD] (entrapment by pannus or suture, inappropriate sizing or positioning, or other)
- Structural deterioration (intrinsic and extrinsic calcification, leaflet perforation or tear, leaflet thickening, or myxomatous degeneration)
- Prosthesis Stenosis
- Prosthesis Regurgitation
- Valve Thrombosis
- Thromboembolism

It is possible that these complications could lead to:

- Reoperation
- Explantation
- Permanent Disability
- Death

The above complications may present clinically with:

- dyspnea
- orthopnea
- exercise intolerance
- syncope
- fever
- abnormal heart murmur
- anemia (including hemolytic anemia)

- low cardiac output
- pulmonary edema
- heart failure
- angina
- myocardial infarction
- stroke

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Bench Testing

i. Biocompatibility Studies

Biocompatibility testing for the ATS 3f® Aortic Bioprosthesis, Model 1000 was conducted in accordance with the requirements of ISO 10993, Biological Evaluations of Medical Devices. Biocompatibility testing and results are provided in the Table 1 below. Hemocompatibility was evaluated and found to be acceptable as demonstrated in the animal study section.

Table 1: Biocompatibility Studies

Test	Objective	Control(s)	Test Article	Results
Initial Evaluation Tests				
Cytotoxicity	To assess the toxicity or irritation potential of materials through the use of isolated cells in vitro.	Negative control is HDPE, reagent control is MEM without test material. Positive control is tin stabilized polyvinyl chloride.	1 – 29 mm valve	No evidence of causing cell lysis or toxicity.
Sensitization	To determine whether a material contains chemicals that cause adverse local or systemic effects after repeated or prolonged	Reagent controls are the saline and cottonseed oil without test material.	2 – 29 mm valves	No evidence of causing delayed dermal contact sensitization in the guinea pig.

Test	Objective	Control(s)	Test Article	Results
	exposure.			
Irritation Test	To estimate the local irritation potential of material injected intradermally.	Reagent controls are the MEM and cottonseed oil without test material.	1 – 29 mm valve	No evidence of significant irritation was detected at the injection site.
Acute Systemic toxicity	To detect leachables that produce systemic toxic effects.	Reagent controls are the MEM and cottonseed oil without test material.	29 mm valve	No mortality or evidence of systemic toxicity.
Pyrogen Test	Evaluates the potential to cause a pyrogenic response or fever when introduced into the cardiovascular system.		8 – 29 mm valves tested	Nonpyrogenic.
Subchronic toxicity	To determine the effects from long-term or multiple exposures.	Reagent control is MEM without test material.	28 – 29 mm valves	Findings were within acceptable limits and were similar between and within test and control treatment group.
Genotoxicity: Gene mutation	To detect mutagens that can directly or indirectly induce genetic damage.	Reagent controls are the MEM and DMSO without test material.	1 – 29 mm valve	Nonmutagenic to the strains. No significant evidence of systemic toxicity.

Table 1: Biocompatibility Studies (cont.)

Test	Objective	Control(s)	Test Article	Results
Genotoxicity: Chromosome aberration	To detect mutagens that can directly or indirectly induce genetic damage.	Negative control is McCoy's 5A medium w/o test material.	6 – 29 mm valves.	Not genotoxic.
Genotoxicity: DNA Damage	To detect mutagens that can directly or indirectly induce genetic damage.	Negative control single strength MEM, Positive control is cyclo-phosphamide (CP).	2 – 29 mm valves	Not genotoxic. No evidence of cellular deformity.
Genotoxicity: DNA Damage	To detect mutagens that can directly or indirectly induce genetic damage.	Negative control is single cultures of the vehicle control consisting of cells exposed to serum-free medium (unexposed to the extraction conditions), and an untreated control consisting of cells plus treatment medium. Positive control is methylmethanesulfonate (MMS) and methyl-cholanthrene (MCA)	4 – 29 mm valves	Negative without metabolic activation and weakly positive with metabolic activation at the TK locus in L5178Y mouse lymphoma cells.
USP Rabbit Muscle Implant	Evaluation of the effect of direct exposure of the test material when implanted in the para-vertebral muscle of rabbits for 2, 6, & 12 weeks.	Negative control is polyethylene negative reference strips. Sponsor control is a commercially available tissue valve.	29 mm valve	Not significant as compared to the sponsor or USP negative control. Microscopically, the test article and sponsor control were moderate irritants as compared to the USP negative control.

Test	Objective	Control(s)	Test Article	Results
Hemolysis, in vitro	To determine the degree of hemolysis (disruption of blood cells) and thrombo-genicity (activation of the coagulation pathway).	Negative control is high density polyethylene. Positive control is sterile water for injection.	2 – 29 mm valves	Non-hemolytic.

Supplementary Evaluation Tests		
Chronic toxicity, Hemocompati-bility	Chronic toxicity evaluated in 20 week sheep implant, Test Report #4, "A Pre-clinical In Vivo Evaluation of Model 1000, Stentless Aortic Bioprosthesis in the Sheep Model"	Sheep implanted with test and control valves were considered healthy after 20 weeks.

ii. Hydrodynamic Performance

Table 2: Hydrodynamic Performance

Test	Sample Size: Model 1000	Sample Size: Control	Pass/Fail Criteria	Results
Pulsatile Flow Pressure Gradient	18 (3 of each size)	2	Pressure Drop to be ≤ Control valve	Pass
Dynamic Regurgitation	3 – 29 mm	1 – 29 mm	Leakage Volume to be ≤ Control valve of equivalent flow area	Pass
Flow Visualization	2 – 19 mm	N/A	Qualitatively visualize downstream flow field	Uniform and symmetric centrally directed systolic flow and no regurgitant jets during diastole
Steady Forward Flow Pressure Gradient	18 (3 of each size)	1 – 19 mm 1 – 29 mm	Pressure Drop to be ≤ to the Control valve and EOA to be ≥ Control valve	Pass
Steady Backflow Leakage	36 (3 of each size) for both 4% and 16% compliant aortas	2 – 19 mm 2 – 29 mm	Leakage rate to be ≤ Control valve	Pass
Verification of Bernoulli Relationship	6 (2 each of the 19 mm, 25 mm and 29 mm)	N/A	Verify Bernoulli relationship could adequately measure pressure gradients	Relationship confirmed
Static Pressure "Burst" Test	3 – 29 mm	N/A	Subject valves to increasing back pressure to determine the pressure the valve can withstand	All valves were pressurized to 42 psig (equivalent to 2,172 mmHg) without any structural failure
Sewing Ring Integrity Test	3 – 29 mm	N/A	Maintenance of structural integrity and function of valve following excessive retro-grade pressures.	Sewing ring and tabs withstood higher pull force than typical cardiovascular suture. Valve withstood axial pull force approximately 5 times greater than force *in vivo* due to blood pressure

iii. Structural Performance

Table 3: Structural Performance

Test	Sample Size: Model 1000	Sample Size: Control	Pass/Fail Criteria	Results
Accelerated Wear	N = 30 (10 each of sizes 19 mm, 25 mm and 29 mm)	n = 6 (2 each of sizes 19 mm, 25 mm and 29 mm)	Wear to be ≤ Control valve	Overall, the Model 1000 compares very favorably to the control valve. The Model 1000 had less structural valve deterioration and less associated regurgitation when compared to the predicate marketed device.

B. Animal Studies

A chronic *in vivo* animal implantation study was conducted using ATS 3f® Aortic Bioprosthesis, Model 1000 valves implanted in healthy sheep. Six sheep received the Model 1000 valve and two (2) sheep received a control valve.

Six (6) sheep that received a Model 1000 test valve survived full-term (i.e. for 20 weeks). All test devices explanted from full-term surviving animals appeared similar. No perivalvular defects were noted. Except for regions of focal mineralization, the leaflets were thin and pliable. Mineralization, when present, was mild and usually centered on the commissural and basal attachment of the leaflets.

One animal that received a control valve survived full-term. The leaflets of the control valve were thin and pliable. The commissural posts of the control valve were stiffened by mineralization, and a perivalvular rent was present below the left coronary ostium. A second animal that received a control valve survived 104 days before expiring due to aortic stenosis leading to congestive heart failure.

In vivo parameters evaluated during the study included physical observations of the status of the animals, surgical implant procedure observations, hematology and blood chemistry measurements (prior to implant and immediately prior to explant), and cardiac output and peak transvalvular gradients obtained by echocardiographic assessment. Post mortem evaluation included explanted valve radiographic assessment for calcium content and distribution, necropsy observations, and histopathologic evaluation of the explanted valve, host tissue and selected organs.

i. Clinical Chemistry and Hematology

Hematology and chemistry results for the test and control animals varied, ranging from slightly elevated to slightly depressed relative to reference values. No

individual out-of-range value was deemed to be clinically significant. The number of study and control subjects was insufficient for statistical analysis.

ii. Hemodynamic Performance

Echocardiography was performed intra-operatively and immediately prior to examination of the valve. The Model 1000 bioprosthesis leaflets appeared to function well, without visible progressive thickening. The measured mean systolic gradients across the bioprostheses were somewhat higher than the prior gradients measured in vitro. This discrepancy may be attributed to the inability to implant a bioprosthesis of the size measured by pre-implant echocardiography. During surgery, a sub-aortic stenosis dictated the implant of a smaller-sized valve than seen echocardiographically for the sheep's native valve.

iii. Histopathology

Animals were sacrificed at approximately 20 weeks (143 – 149 days) post-implant. Selected systemic organs were examined for their gross and microscopic morphology. All animals appeared healthy and in good condition at the time of sacrifice with the exception of one animal with unexplainable non-symptomatic centrolobular congestion of the liver. Pathology of the experimental valve compared favorably with that of the control valve used in the study.

Some Model 1000 bioprostheses exhibited minute regions of mild focal mineralization at the basal and commissural attachment regions. The leaflets remained thin and pliable. The explanted control valve leaflets were also thin and pliable, but the commissural areas were stiffened by mineralization. Note that the ATS 3f® Aortic Bioprosthesis, Model 1000 valve consists only of leaflets and commissural tabs while the control valve also consists of porcine aorta material.

C. Sterilization

The device is provided sterile. Final sterilization is achieved with a sterilant formulation based on glutaraldehyde and a low molecular weight alcohol that also provides germicidal action until the valve is ready for use. The sterilization process has been validated to assure a sterility assurance level (SAL) of 10^{-6}.

D. Shelf Life

The shelf life for the ATS 3f® Aortic Bioprosthesis, Model 1000 was validated to ensure that both the package integrity and the product integrity are maintained for two (2) years.

i. Package Integrity

Packaging integrity studies utilized both real-time and accelerated aged test samples. Physical and sterility testing were performed after exposure to glutaraldehyde in elevated temperature conditions, and after simulated shipping process to ensure the integrity of the packaging. Packaging integrity testing has demonstrated that the integrity of the package used with the Model 1000 is maintained for two years.

ii. Product Integrity

Integrity of the finished Model 1000 device was evaluated after accelerated aging for 1, 2 years and after real time aging to 2 years. Test methods used to evaluate shelf life included visual inspection, Ninhydrin assay for free amino groups, shrink temperature testing for stability of cross-linkage in the fixed tissue, valve performance, biocompatibility of immediate packaging container and sterility testing. All real time and accelerated aged units were shown to have maintained sterility and to have met the necessary performance specifications. Based on the results, product integrity of the Model 1000 has been established in support of a 2-year shelf life.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of aortic valve replacement with the ATS 3f® Aortic Bioprosthesis, Model 1000 for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves in the US under IDE # G010284. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between October 3, 2001 and December 31, 2005. The database for this PMA/PMA supplement reflected data collected through November 22, 2006 and included 405 subjects. There were 23 investigational sites.

The study was a prospective, multi-center, one-arm, non-randomized open label clinical study. Four outcome variables; changes in patients' NYHA functional classification, blood data, occurrences of cardiovascular complications and hemodynamic performance were used to evaluate the safety and effectiveness of the valve. Additionally all safety and effectiveness data for the device were compared to literature-based control data.

An echo core laboratory was used to develop protocol requirements, review echo tapes and assess/interpret patient echo data. The core lab cardiologist interpretations of all echocardiograms were used for the final analysis.

A Data Safety Monitoring Board (DSMB) comprised of two cardiovascular surgeons, one cardiologist, one biostatistician and one nurse practitioner, all of whom were independent of ATS Medical and the clinical investigators conducting the clinical study was assembled. The DSMB was given autonomy to act on behalf of the subjects and was charged with examining any and all safety issues related to this study (e.g., adverse events and adverse device events).

The control group was a historical control group, the study results were compared to the Objective Performance Criteria (OPC), listed in the 1994 FDA Draft Replacement Heart Valve Guidance and to data from literature-based historical controls).

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the ATS 3f® Aortic Bioprosthesis, Model 1000 study was limited to patients who met the following inclusion criteria.

   - required *isolated aortic* valve replacement with or without concomitant procedures such as coronary artery bypass or another valve reconstruction.
   - sufficiently ill to warrant replacement of his/her diseased natural or prosthetic valve, based on standard cardiovascular diagnostic workups.

   Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

   - Under 21 years of age
   - pregnant (urine HCG test result positive), or lactating.
   - active endocarditis.
   - congenital bicuspid aortic anatomy.

2. Follow-up Schedule
   All subjects were scheduled to return for follow-up examinations at discharge or 30 days (which ever came last), 3-6 month, 1 year postoperatively and annually thereafter.

   The preoperative and postoperative objective parameters measured during the study are listed in the table below. Adverse events and complications were recorded at all visits.

Table 4. Study Evaluation Schedule and Requirement (X=required)

Requirements	Schedule					
	Pre-op	Operative	Post-op < 30 days/ Discharge (whichever comes last)	Post-Op 3-6 Months	Post-Op 1 year	Annually
Demographics	X					
History / Risk Factors	X					
PT Status / Follow-up			X	X	X	X
NYHA Class	X			X	X	X
Cardiac Rhythm	X		X	X	X	X
Blood Data	X			X	X	
Echocardiogram	Optional	Optional	X	X	X	X
Complications		X	X	X	X	X
Operative Info.		X				
Anticoagulant Therapy	X		X	X	X	X

The results are shown in the tables that follow, summarizing safety and effectiveness.

3. Clinical Endpoints

With regards to safety, the following endpoints were used for the Model 1000 valve clinical study: death (all, valve-related/unknown, and non-valve-related), valvular thrombosis, valve-related thromboembolism, bleeding (all and major), perivalvular leak (all and major), endocarditis, hemolysis, structural valve deterioration, nonstructural valve dysfunction, reoperation, and explant. Blood data consisted of white blood cell count, red blood cell count, hemoglobin, hematocrit, reticulocyte count, platelet count, serum lactate dehydrogenase (LDH), serum haptoglobin, serum creatinine, and serum alkaline phosphatase. Data on anti-thromboembolic therapy were also collected.

With regards to effectiveness, the following endpoints were used for the Model 1000 valve clinical study: New York Heart Association (NYHA) functional classification and the hemodynamic parameters peak gradient (PG), mean gradient (MG), effective orifice area (EOA), effective orifice area index (EOAI), performance index (PI), cardiac output (CO), cardiac index (CI), and valvular regurgitation.

With regard to success/failure criteria, the primary efficacy criterion is the improvement in NYHA ratings compared to their baseline values and the hemodynamic performance of the valve as determined by Doppler echocardiography and the primary safety objective is to show that the complication rates with the valve are less than two times the OPC established by

the FDA (in the Draft Guidance dated October 19, 1994) for severe complications.

B. Accountability of PMA Cohort

At the time of database lock, all 405 subjects enrolled in PMA study were eligible for analysis at discharge and at up to four years postoperatively over the course of 909.4 patient years of follow-up..

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a randomized control study performed in the US.

A total of 405 patients at the 23 centers were implanted with the Model 1000 bioprosthesis between October 3, 2001 and December 31, 2005. The study population included 240 male (59.3%) and 165 female (40.7%) patients. Patients were evaluated preoperatively, within 30 days post-operatively, at 3 to 6 months, 11 to 14 months and annually. Patients were monitored throughout the postoperative period for possible adverse events. The cumulative follow-up was 909.4 patient-years with a mean of 2.3 (SD = 1.1 years, range of follow-up = 0.01 to 4.4 years).

Table 5 presents preoperative patient demographics and risk factors for the study cohort. Sixty-five (65) percent of the patients were 70 years old or greater at implant and the mean age was 70.7 years. Fifty-seven (57) percent of the patients were in NYHA Functional Classification III or IV.

Table 5: Pre-Operative Clinical Data *

Variable	Category	n	%(n/N) N=405
Age at Implant (Years)	20-29	1	0.3
	30-39	8	2.0
	40-49	11	2.8
	50-59	26	6.6
	60-69	92	23.2
	70-79	197	49.6
	80 & over	62	15.6
Age (range [years])			23-93
Mean Age at Implant		70.7 ± 10.5 Years	

Variable	Category	n	%(n/N) N=405
Gender	Female	158	39.8
	Male	239	60.2
NYHA Classification	I	23	5.8
	II	149	37.5
	III	193	48.6
	IV	32	8.1
Valve Dysfunction	Stenosis	302	76.1
	Insufficiency	15	3.8
	Mixed	79	19.9
	Prosthesis Dysfunction	1	0.3

N = total number of study patients; n = number of patients in each category.
* Size 19mm valves were studied but data for this size are not included in this table because of the limited clinical data available at the time of PMA evaluation.

D. Safety and Effectiveness Results

The safety endpoints captured in this study were mortality and valve related morbidity. The effectiveness endpoints in this study were New York Heart Association (NYHA) functional classification and hemodynamic assessments obtained by echocardiography.

1. Safety Results

The analysis of safety was based on the treatment cohort of 405 patients available over the course of 909.4 patient years of follow-up. The key safety outcomes/adverse events for this study are presented below in table 6.

The adverse event rates for aortic valve replacement are presented in Table 6. The data is presented as % Operative events (those that occurred on or before day 30 post-implant), Linearized Rate (%/patient year) for the total events that occurred and "freedom from event" as an Actuarial analysis at 1 and 3 years post implant. The rates are also compared to the OPC x 2 for the appropriate respective parameters.

Table 6: Principal Safety Parameters

All patients analyzed, N = 405; Cumulative follow-up = 909.4 patient years and 876.9 late patient-years

Adverse Event/ Complication	Operative (%)	Linearized Rate (%/Pt-Yr)	Upper 95% Confidence Interval	OPC x 2 (%/Pt-Yr)	Actuarial Analysis at 1 Year Post-op (95% CI)	Actuarial Analysis at 3 Years Post-op (95% CI)
Mortality (All)	3.2	5.1	6.6	N/A	92.1 (89.3,94.9)	83.7 (79.5,87.9)
Mortality (Valve-Related)	0.3	0.3	0.9	N/A	99.2 (98.2,100.0)	98.7 (97.3,100.0)
Reoperation (including Explant)	0.3	0.0	0.0	N/A	99.7 (99.2,100.0)	99.7 (99.2,100.0)
Explant	0.0	1.6	2.5	N/A	98.2 (96.8,99.6)	96.1 (93.9,98.3)
Structural Deterioration	0.0	0.0	0.0	N/A	100.0 (100.0,100.0)	100.0 (100.0,100.0)
Hemolysis	0.0	0.0	0.0	N/A	100.0 (100.0,100.0)	100.0 (100.0,100.0)
Non-Structural Dysfunction	0.5	0.3	0.9	N/A	99.5 (98.7,100.0)	98.6 (97.2,100.0)
Thromboembolism (Valve-Related)	1.7	2.2	3.2	5.0	94.9 (92.7,97.1)	93.2 (90.6,95.8)
Valve Thrombosis	0.0	0.0	0.0	0.4	100.0 (100.0,100.0)	100.0 (100.0,100.0)
Bleeding Events (All)	2.0	1.3	2.1	2.8	96.1 (94.1,98.1)	95.2 (93.0,97.4)
Bleeding Events (Major)	1.7	0.8	1.5	1.8	97.2 (95.6,98.8)	96.5 (94.5,98.5)
Perivalvular leak (All)	1.0	1.0	1.8	2.4	97.7 (96.1,99.3)	96.4 (94.4,98.4)
Perivalvular leak (Major)	0.0	0.3	0.9	1.2	99.2 (98.2,100.0)	99.2 (98.2,100.0)
Endocarditis	0.0	1.0	1.8	2.4	99.2 (98.4,100.0)	97.5 (95.7,99.3)

pt-yr = patient-year; OPC = Objective Performance Criteria as established by the US FDA; CI = Confidence Interval; N/A = not applicable.

2. Effectiveness Results

The analysis of effectiveness was based on the 405 patients evaluable over the course of 909.4 patient years of follow-up. Key effectiveness outcomes are presented in tables 7 to 9.

Table 7 presents the pre-operative vs. 3-6 months, 1 year, 2 year, 3 year and 4 year NYHA Classification comparisons.

Table 7: NYHA Functional Classification Change from Baseline *

Pre-op NYHA Class	1 Year NYHA (N = 327)							
	I		II		III		IV	
	n	%	n	%	n	%	n	%
I	20	6.1	1	0.3	0	0.0	0	0.0
II	73	2.2	47	14.4	5	1.5	0	0.0
III	102	31.2	45	13.8	8	2.4	0	0.0
IV	16	4.9	8	2.4	2	0.6	0	0.0
Total	211	64.5	101	3.1	15	4.6	0	

Pre-op NYHA Class	2 Years NYHA (N = 266)							
	I		II		III		IV	
	n	%	n	%	n	%	n	%
I	17	6.4	1	0.4	0	0.0	0	0.0
II	53	19.9	37	13.4	4	1.5	1	0.4
III	79	29.7	41	15.4	9	3.4	0	0.0
IV	16	6.0	5	1.9	2	0.8	1	0.4
Total	165	62.0	84	31.6	15	5.6	2	0.8

Pre-op NYHA Class	3 Years NYHA (N = 161)							
	I		II		III		IV	
	n	%	n	%	n	%	n	%
I	9	5.6	0	0.0	0		0	0.0
II	32	19.9	12	7.4	2	1.2	0	0.0
III	60	37.3	22	13.7	7	4.3	0	0.0
IV	11	6.8	5	3.7	1	0.6	0	0.0
Total	112	69.6	39	24.2	10	6.2	0	0.0

Pre-op NYHA Class	4 Years NYHA (N = 44)							
	I		II		III		IV	
	N	%	n	%	n	%	n	%
I	3	6.8	1	2.3	0	0.0	0	0.0
II	5	11.4	3	6.8	0	0.0	0	0.0
III	17	38.6	5	11.4	2	4.5	0	0.0
IV	4	9.1	4	9.1	0	0.0	0	0.0
Total	29	65.9	13	29.5	2	4.5	0	0.0

* Size 19mm valves were studied but data for this size are not included in this table because of the limited clinical data available at the time of PMA evaluation.

Table 8 presents the prevalence and severity of aortic regurgitation by valve size at discharge and 1 year.

Table 8: Prevalence and Severity of Aortic Regurgitation *

			21 mm		23 mm		25 mm		27 mm		29 mm	
Interval	N	Severity	n	%	n	%	n	%	n	%	n	%
Discharge	353	0 None/Trace	35	72.9	65	68.4	70	70.0	51	76.1	29	67.4
		1+ Mild	7	14.6	21	22.1	18	18.0	15	22.4	8	18.6
		2+ Moderate	1	2.1	1	1.1	4	4.0	0	0.0	0	0.0
		3+ Moderate/Severe	0	0.0	0	0.0	1	1.0	0	0.0	0	0.0
		4+ Severe	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Regurgitation Not Evaluable	5	10.4	8	8.4	7	7.0	1	1.5	6	14.0
3-6 Months	333	0 None/Trace	29	69.0	58	69.9	72	75.8	53	77.9	34	75.5
		1+ Mild	12	28.6	20	24.1	17	17.9	13	19.1	9	20.0
		2+ Moderate	1	2.4	4	4.8	3	3.2	0	0.0	2	4.4
		3+ Moderate/Severe	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		4+ Severe	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Regurgitation Not Evaluable	0	0.0	1	1.2	3	3.2	2	2.9	0	0.0
1 Year	328	0 None/Trace	33	80.5	60	73.2	69	76.7	51	75.0	34	72.3
		1+ Mild	8	19.5	18	22.0	18	20.0	14	20.6	9	19.1
		2+ Moderate	0	0.0	2	2.4	3	3.3	2	2.9	2	4.3
		3+ Moderate/Severe	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		4+ Severe	0	0.0	0	0.0	0	0.0	0	0.0	1	2.1
		Regurgitation Not Evaluable	0	0.0	2	2.4	0	0.0	1	1.5	1	2.1
2 Years	258	0 None/Trace	24	80.0	43	70.5	49	72.1	41	70.7	25	61.0
		1+ Mild	4	13.3	9	14.8	13	19.1	13	22.4	11	26.8
		2+ Moderate	0	0.0	4	6.6	5	7.4	3	5.2	2	4.9
		3+ Moderate/Severe	0	0.0	0	0.0	0	0.0	0	0.0	1	2.4
		4+ Severe	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Regurgitation Not Evaluable	2	6.7	5	8.2	1	1.5	1	1.7	2	4.9

Interval	N	Severity	21 mm		23 mm		25 mm		27 mm		29 mm	
			n	%	n	%	n	%	n	%	n	%
3 Years	146	0 None/Trace	12	66.7	23	65.7	27	75.0	20	69.0	19	67.9
		1+ Mild	5	27.8	7	20.0	4	11.1	5	17.2	3	10.7
		2+ Moderate	1	5.6	1	2.9	1	2.8	0	0.0	4	14.3
		3+ Moderate/Severe	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		4+ Severe	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Regurgitation Not Evaluable	0	0.0	4	11.4	4	11.1	4	13.8	2	7.1
4 Years	37	0 None/Trace	3	75.0	1	25.0	6	66.7	8	66.7	6	75.0
		1+ Mild	1	25.0	1	25.0	2	22.2	2	16.7	2	25.0
		2+ Moderate	0	0.0		10.0	1	11.1	2	16.7	0	0.0
		3+ Moderate/Severe	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		4+ Severe	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Regurgitation Not Evaluable	0	0.0	2	50.0	0	0.0	0	0.0	0	0.0

* Size 19mm valves were studied but data for this size are not included in this table because of the limited clinical data available at the time of PMA evaluation.

Table 9 presents hemodynamic data (Mean Pressure Gradient and Effective Orifice Area) by valve size at discharge and 1 year.

Table 9: Hemodynamic Data: Mean Gradient and Effective Orifice Area *

Endpoint	Discharge	1 Year
Mean pressure gradient (mmHg)	**(N=323)**	**(N=312)**
21 mm	16.2 ± 7.1	16.4 ± 5.5
23 mm	15.8 ± 7.0	14.8 ± 6.0
25 mm	12.5 ± 5.0	11.5 ± 4.8
27 mm	10.4 ± 5.0	10.3 ± 4.4
29 mm	7.7 ± 2.7	7.9 ± 3.4
Effective Orifice Area (cm^2)	**(N=240)**	**(N=248)**
21 mm	1.3 ± 0.4	1.2 ± 0.3
23 mm	1.3 ± 0.4	1.3 ± 0.3
25 mm	1.6 ± 0.4	1.6 ± 0.4
27 mm	1.9 ± 0.5	1.9 ± 0.5
29 mm	2.7 ± 0.9	2.4 ± 0.7

* Size 19mm valves were studied but data for this size are not included in this table because of the limited clinical data available at the time of PMA evaluation.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: gender.

In the ATS 3f® Aortic Bioprosthesis, Model 1000 clinical study, 59.3% of the patients were male (240/405) and 40.7% were female (165/405). The gender distribution is consistent with the incidence within the aortic heart valve replacement population in the United States. No patient selection bias based on gender could be identified in the study population.

An analysis of pre-operative risk factors showed no significant differences due to gender; thus no gender bias was found.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

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 Device panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The clinical data from the ATS 3f® Aortic Bioprosthesis, Model 1000 study cohort of 405 patients met the criteria for safety specified in the study protocol. The primary safety endpoint for the study was analysis of adverse events/complication rates in relation to the Objective Performance Criteria (OPC) established by the FDA. In the ATS 3f® Aortic Bioprosthesis, Model 1000 study, the adverse event rates for these major safety variables were below the established standard of twice the FDA's Objective Performance Criteria for a tissue valve and were comparable to similar marketed devices. Mortality, reoperation and explant rates also support the safety of the valve.

B. Effectiveness Conclusions

The primary parameters for effectiveness in the study were hemodynamic performance and functional improvement in post-operative NYHA Classification relative to pre-operative status. This study has demonstrated that the ATS 3f® Aortic Bioprosthesis Model 1000 improved NYHA Functional Classification postoperatively. Echocardiography at discharge through four years of follow-up

showed the peak and mean gradients to be within the expected ranges for a tissue valve. The majority of patients with the valve had none/trace to mild (0 to 1+) regurgitation by echocardiography from discharge through up to four years of follow-up.

C. **Overall Conclusions**

The preclinical and clinical studies data in this application support the reasonable assurance of safety and effectiveness of the ATS 3f® Aortic Bioprosthesis, Model 1000, available in sizes 21mm, 23mm, 25mm, 27mm, and 29mm, when used in accordance with the approved labeling. The benefits of improved hemodynamics were demonstrated by the improvement in NYHA functional classification of the patients at the follow-up assessment period.

The results of the ATS 3f® Aortic Bioprosthesis, Model 1000, clinical study support and provide evidence to the safety, effectiveness and favorable risk/benefit ratio of the use of the ATS 3f® Aortic Bioprosthesis, Model 1000 for aortic valve replacement.
Note that the size 19mm ATS 3f® Aortic Bioprosthesis, Model 1000, was included in the in-vitro preclinical studies and the clinical studies. However, at the time of PMA application submission, the number of patients implanted with the size 19mm valve, as well as length of follow-up, were insufficient to support approval for the size 19mm valve.

XIII. CDRH DECISION

CDRH issued an approval order on October 30, 2008. The final conditions of approval cited in the approval order are described below.

ATS has agreed to implement a clinical post-approval study to determine if there is an increased incidence of long-term aortic regurgitation in patients ≤60 years of age who are undergoing isolated aortic valve replacement of his/her native aortic valve or replacement of a failed prosthesis, and are implanted with the ATS 3f® Aortic Bioprosthesis, Model 1000. The study design is a single-arm, multi-center study enrolling a new set of patients. Long-term safety performance will be gauged by the echocardiographically defined aortic regurgitation-free (less than moderate) proportion, which will be compared to a proportion of 92% with a non-inferiority margin of 7.5%. Regurgitation-free proportions will also be presented by valve size in a descriptive analysis. A total of 127 subjects will be enrolled to allow for an adequate number of patients implanted with the study valve to achieve 606 patient-years (i.e., minimum of 101 patients followed for a minimum of 6 years).

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.