SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Replacement Heart Valve
Device Trade Name:	Edwards SAPIEN™ Transcatheter Heart Valve model 9000TFX, 23 and 26mm, and accessories (RetroFlex 3™ Delivery System, models 9120FS23 and 9120FS26 RetroFlex™ Balloon Catheter, models 9120BC20 and 9120BC23 Crimper, models 9100CR23 and 9100CR26)
Applicant Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 9261
Date of Panel Recommendation:	July 20, 2011
PMA Application Number:	P100041
Date of FDA Notice of Approval:	November 2, 2011
Expedited:	Granted expedited review status on November 24, 2010 because the SAPIEN device offers significant, clinically meaningful advantages over existing therapies, and the SAPIEN represents a breakthrough technology that provides a clinically meaningful option in a patient population with few options.

II. INDICATIONS FOR USE

The Edwards SAPIEN Transcatheter Heart Valve (THV), model 9000TFX, sizes 23mm and 26mm, is indicated for transfemoral delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.

III. CONTRAINDICATIONS

The bioprosthesis and delivery system are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

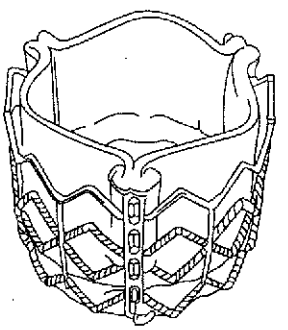
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the labeling for the Edwards SAPIEN Transcatheter Heart Valve with the RetroFlex 3 Delivery System, the labeling for the RetroFlex Balloon Catheter, and the labeling for the Crimper (Instructions for Use).

V. DEVICE DESCRIPTION

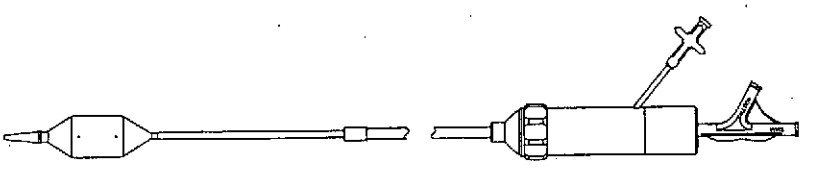
The Edwards SAPIEN Transcatheter Heart Valve (bioprosthesis), shown in Figure 1, is comprised of a balloon-expandable, radiopaque, stainless steel (316L) frame, three bovine pericardial tissue leaflets, and a polyethylene terephthalate (PET) fabric. The bioprosthesis is treated according to the Carpentier-Edwards ThermaFix process, packaged, and terminally sterilized in glutaraldehyde.

Figure 1: Edwards SAPIEN Transcatheter Heart Valve



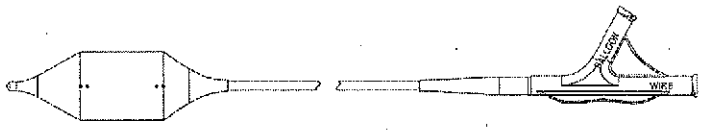
The RetroFlex 3 Delivery System, shown in Figure 2, includes a rotating wheel within the handle for articulation of flex catheter, a tapered tip at the distal end of the delivery system to facilitate crossing the native valve, a balloon for deployment of the bioprosthesis, and radiopaque markers.

Figure 2: RetroFlex 3 Delivery System



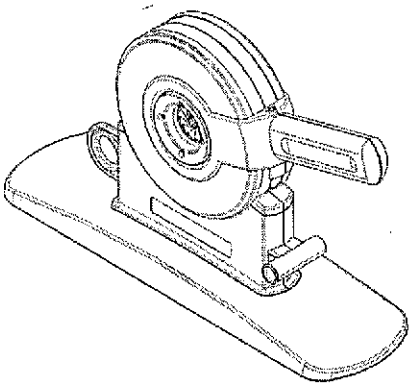
The RetroFlex Balloon Catheter, shown in Figure 3, is used to pre-dilate stenotic cardiac valves. The device consists of a shaft and balloon with radiopaque markers indicating working length of the balloon. At the proximal end of the device, there is a standard "Y-connector" for balloon inflation and guidewire insertion.

Figure 3: RetroFlex Balloon Catheter



The Crimper, shown in Figure 4, is comprised of a housing and a compression mechanism, creating an aperture that is opened and closed by means of a handle located on the housing. The crimper includes a balloon gauge to verify diameter of an inflated balloon catheter and a crimp gauge to verify collapsed diameter of the device.

Figure 4: Crimper



VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternatives for patients deemed to be at excessive risk for surgery, or non-operable (non-surgical) include temporary relief using a percutaneous technique called balloon aortic valvuloplasty (BAV) or medical therapy (no obstruction-relieving intervention).

VII. MARKETING HISTORY

Commercial distribution of the SAPIEN Transcatheter heart valve Model 9000TFX and accessories outside the United States (U.S.) began in October 2007. Currently, the device is approved for distribution in the 27 member states under the European Union, Croatia, Iran, Israel, Jordan, Kuwait, Monaco, Norway, Russia, Saudi Arabia, Singapore, South Africa, Switzerland, Thailand and Turkey. The SAPIEN valve and accessories have not been withdrawn from the market in any country for any reason related to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The adverse events listed below are associated with access complications associated with catheterization or valvuloplasty, and events associated with local and/or general anesthesia.

- Death
- Stroke/transient ischemic attack or neurological deficit
- Paralysis
- Permanent disability
- Respiratory insufficiency or respiratory failure
- Hemorrhage requiring transfusion or intervention
- Cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention
- Pericardial effusion or cardiac tamponade
- Embolization including air, calcific valve material or thrombus
- Infection including septicemia and endocarditis
- Heart failure
- Myocardial infarction
- Renal insufficiency or renal failure
- Conduction system injury (defect) which may require a permanent pacemaker
- Arrhythmia
- Retroperitoneal bleed
- Femoral AV fistula or pseudoaneurysm
- Reoperation
- Peripheral ischemia or nerve injury
- Restenosis
- Pulmonary edema
- Pleural effusion
- Bleeding
- Anemia
- Abnormal lab values (including electrolyte imbalance)
- Hypertension or hypotension;
- Allergic reaction to anesthesia or to contrast media
- Hematoma
- Syncope
- Pain or changes at the access site
- Exercise intolerance or weakness
- Inflammation
- Angina
- Heart murmur
- Fever

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Additional potential risks specifically associated with the use of the bioprosthesis include, but may not be limited to the following:

- Cardiac arrest
- Cardiogenic shock
- Emergency cardiac surgery
- Cardiac failure or low cardiac output
- Coronary flow obstruction/transvalvular flow disturbance
- Device thrombosis requiring intervention
- Valve thrombosis
- Device embolization
- Device migration or malposition requiring intervention Valve deployment in unintended location
- Valve stenosis
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflets retraction, stent creep, suture line disruption of components of a prosthetic valve, thickening, stenosis, or other)
- Device degeneration
- Paravalvular or transvalvular leak
- Valve regurgitation
- Hemolysis
- Device explants
- Nonstructural dysfunction
- Non-emergent reoperation

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Testing

In vitro studies were performed for the Edwards SAPIEN Transcatheter Heart Valve Model 9000TFX and non-implantable accessories as recommended in the ISO 5840: *Cardiovascular Implants-Cardiac Valve Prostheses* (2005) standard.

Biocompatibility Studies

Toxicology and biocompatibility testing for the SAPIEN Transcatheter Heart Valve Model 9000TFX and accessories was conducted in accordance with Good Laboratory Practices (21 CFR §58) and ISO 10993-1: 2003 *Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.*

Summaries of the test results for the SAPIEN Transcatheter Heart Valve Model 9000TFX are provided in Table 1. Summaries of the test results for the RetroFlex 3 Delivery System, RetroFlex Balloon Catheter, and Crimper are provided in Tables 2, 3, and 4, respectively. Test samples for the studies consisted of all patient-contacting portions of the devices (direct and indirect contact) after all manufacturing processes including sterilant exposure. All results were found to be acceptable.

Table 1: Summary of Biocompatibility Testing – SAPIEN Valve Model 9000TFX		
Test	**Purpose**	**Results**
Cytotoxicity: Percent Inhibition of Cell Growth	Determine whether test article extract would inhibit cell growth	Test article found to be non-inhibitory to cell growth at a sample concentration representative of the device's clinical application. Inhibitory to cell growth at elevated sample concentrations.
Cytotoxicity: Medium Eluate Method (MEM)	Determine whether test article extracts would cause cytotoxicity and cell lysis	Test article sample was non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control.
Cytotoxicity: Agar Overlay Test	Determine whether solid samples of test article would cause cytotoxicity and cell lysis.	Solid samples of the stent frame were non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control. Cytotoxicity was observed in solid samples of the cloth, suture, and tissue material due to glutaraldehyde and formaldehyde residuals present in the solid sample.
Sensitization: Guinea Pig Maximization	Investigate the potential for delayed dermal contact sensitization.	No irritation was present on any of the test or control animals at 24 or 48 hour readings using saline and vegetable oil extracts. Non-sensitizing.
Irritation/Intracutaneous Toxicity: Rabbit Intracutaneous Reactivity	Determine whether test article extracts would cause local dermal irritation or toxic effects	No evidence of irritation or abnormal effects over a 72 hour period as compared to negative controls.
Systemic Toxicity: USP Mouse Systemic Injection	Determine whether test article extracts would cause acute systemic toxicity	No weight differences or observed systemic effects as compared to negative controls over 72 hour test period.
Systemic Toxicity: Material Mediated (Rabbit) Pyrogen Test	Determine the presence of chemical pyrogens in test article extracts by measuring temperature rise in intravenously injected rabbits.	No temperature rise or abnormalities in any test or control animals.
Implantation Subacute/Subchronic Toxicity Chronic Toxicity	Determine whether the test article would cause systemic toxicity affects after 7, 30, and 90 days intramuscular implantation in rabbits.	No microscopic evidence of cytotoxicity.
Genotoxicity: Ames Test – Plate Incorporation	Determine whether test article extracts would cause mutagenic changes in five *S. typhimurium* strains	Test article extracts demonstrated no mutagenic potential under both the activated and non-activated conditions.
Genotoxicity: Chromosomal Aberration Assay	Determine whether test article extracts would cause genotoxicity in Chinese Hamster ovary cells	Test article extracts demonstrated no mutagenic potential under both the activated and non-activated conditions.

Table 1: Summary of Biocompatibility Testing – SAPIEN Valve Model 9000TFX		
Test	**Purpose**	**Results**
Genotoxicity: Mouse Micronucleus	Determine whether test article extracts would cause genotoxic changes as determined by induced micronucleated polychromatic erythrocytes	Test article extracts were determined to be non-mutagenic.
Hemocompatibility: Hemolysis	Determine whether the test article would cause hemolysis *in vitro* and determine the degree of inhibition or promotion of clotting time	No hemolytic effects observed under static conditions for both extract and solid samples. Material's extract did not adversely affect the clotting time and was determined to be compatible with plasma.

Table 2: Summary of Biocompatibility Testing – RetroFlex 3 Delivery System		
Test	**Purpose**	**Results**
Cytotoxicity: Medium Eluate Method (MEM)	Determine whether test article extracts would cause cytotoxicity and cell lysis	Test article sample was non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control.
Cytotoxicity: Agar Overlay Test	Determine whether solid samples of test article would cause cytotoxicity and cell lysis	Solid samples of test articles were non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control.
Sensitization: Guinea Pig Maximization	Investigate the potential for delayed dermal contact sensitization	No irritation was present on any of the test or control animals at 24 or 48 hour readings using saline and vegetable oil extracts. Non-sensitizing.
Irritation/Intracutaneous Toxicity: Rabbit Intracutaneous Reactivity	Determine whether test article extracts would cause local dermal irritation or toxic effects	No evidence of irritation over a 72 hour period as compared to negative controls.
Systemic Toxicity: USP Mouse Systemic Injection	Determine whether test article extracts would cause acute systemic toxicity	No weight differences or observed systemic effects as compared to negative controls over 72 hour test period.
Systemic Toxicity: Material Mediated (Rabbit) Pyrogen Test	Determine the presence of chemical pyrogens in test article extracts by measuring temperature rise in intravenously injected rabbits.	Temperature rise of $\leq 0.1°C$ and no abnormalities in any test or control animals.
Hemocompatibility: Hemolysis	Determine whether the test article would cause hemolysis *in vitro* and determine the degree of inhibition or promotion of clotting time	No hemolytic effects observed under static conditions for both extract and solid samples. Material's extract did not adversely affect the clotting time and was determined to be compatible with plasma.

Table 2: Summary of Biocompatibility Testing – RetroFlex 3 Delivery System		
Test	**Purpose**	**Results**
Hemocompatibility: Complement Activation	Evaluate the test article's potential to activate the C3 and C5 complement system	Test article was determined to be hemocompatible and not at risk to activate complement at a level of concern in a clinical application. Results equivalent to negative control.

Table 3: Summary of Biocompatibility Testing – RetroFlex Balloon Catheter		
Test	**Purpose**	**Results**
Cytotoxicity: Medium Eluate Method (MEM)	Determine whether test article extracts would cause cytotoxicity and cell lysis	Test article sample was non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control.
Cytotoxicity: Agar Overlay Test	Determine whether solid samples of test article would cause cytotoxicity and cell lysis.	Solid samples of test articles were non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control.
Sensitization: Guinea Pig Maximization	Investigate the potential for delayed dermal contact sensitization.	No irritation was present on any of the test or control animals at 24 or 48 hour readings using saline and vegetable oil extracts. Non-sensitizing.
Irritation/Intracutaneous Toxicity: Rabbit Intracutaneous Reactivity	Determine whether test article extracts would cause local dermal irritation or toxic effects	No evidence of irritation or abnormal effects over a 72 hour period as compared to negative controls.
Systemic Toxicity: USP Mouse Systemic Injection	Determine whether test article extracts would cause acute systemic toxicity	No weight differences or observed systemic effects as compared to negative controls over 72 hour test period.
Systemic Toxicity: Material Mediated (Rabbit) Pyrogen Test	Determine the presence of chemical pyrogens in test article extracts by measuring temperature rise in intravenously injected rabbits.	Temperature rise of $\leq 0.5°C$ and no abnormalities in any test or control animals.
Hemocompatibility: Hemolysis	Determine whether the test article would cause hemolysis *in vitro* and determine the degree of inhibition or promotion of clotting time	No hemolytic effects observed under static conditions for both extract and solid samples. Material's extract did not adversely affect the clotting time and was determined to be compatible with plasma.
Hemocompatibility: Complement Activation	Evaluate the test article's potential to activate the C3 and C5 complement system	Test article was determined to be hemocompatible and not at risk to activate complement at a level of concern in a clinical application. Results equivalent to negative control.

Table 4: Summary of Biocompatibility Testing – Crimper		
Test	**Purpose**	**Results**
Cytotoxicity: Medium Eluate Method (MEM)	Determine whether test article extracts would cause cytotoxicity and cell lysis	Test article sample was non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control.
Sensitization: Guinea Pig Maximization	Investigate the potential for delayed dermal contact sensitization.	No irritation was present on any of the test or control animals at 24 or 48 hour readings using saline and vegetable oil extracts. Non-sensitizing.
Irritation/Intracutaneous Toxicity: Rabbit Intracutaneous Reactivity	Determine whether test article extracts would cause local dermal irritation or toxic effects	No evidence of irritation or abnormal effects over a 72 hour period as compared to negative controls.

SAPIEN Valve Hydrodynamic Performance

In vitro hydrodynamic performance studies of the SAPIEN Model 9000TFX bioprosthesis (test valve) were completed to evaluate performance under steady and pulsatile flow testing conditions. Valves were evaluated after nominal deployment and after deployment into irregular shapes (under deployed, oval deployed, and over deployed). The studies were conducted in accordance with the ISO 5840: Cardiovascular Implants-Cardiac Valve Prostheses (2005) standard. Reference articles for the nominally deployed SAPIEN valve studies consisted of commercially available aortic valves; reference articles for the irregular studies consisted of nominally deployed SAPIEN valves. A matrix of the tests performed and corresponding results is provided in Table 5.

Table 5: Hydrodynamic Testing and Results			
Test	**Purpose/Objective**	**Test/Reference Articles**	**Results**
Steady Forward Flow	To determine the pressure drop at various steady forward flow rates.	Nominal Test: Size 23mm & 26mm Reference: Size 23mm & 27mm Irregular Test: Irregular SAPIEN size 23mm & 26mm Reference: Nominal SAPIEN size 23mm &, 26mm	The SAPIEN valve offers acceptable hemodynamics with pressure gradients and effective orifice areas that are comparable to those offered by the reference valves.

Table 5: Hydrodynamic Testing and Results			
Test	**Purpose/Objective**	**Test/Reference Articles**	**Results**
Steady Backflow Leakage	To determine the leakage rate at various steady back flow pressures.	Nominal Test: Size 23mm & 26mm Reference: Size 23mm & 27mm Irregular Test: Irregular SAPIEN size 23mm & 26mm Reference: Nominal SAPIEN size 23mm &, 26mm	The SAPIEN valve offers satisfactory performance in terms of its competency to prevent significant transvalvular aortic back-flow during the diastolic phase.
Pulsatile Flow Pressure Drop	To determine pressure drop and effective orifice area performance under pulsatile flow conditions.	Nominal Test: Size 23mm & 26mm Reference: Size 23mm & 27mm Irregular Test: Irregular SAPIEN size 23mm & 26mm Reference: Nominal SAPIEN size 23mm &, 26mm	The SAPIEN valve offers acceptable hydrodynamics with a larger effective orifice area than those required by the ISO 5840:2005 acceptance criteria for aortic valves, and similar pressure drop to the reference valves.
Pulsatile Flow Regurgitation	To determine regurgitation performance under pulsatile flow conditions.	Nominal Test: Size 23mm & 26mm Reference: Size 23mm & 27mm Irregular Test: Irregular SAPIEN size 23mm & 26mm Reference: Nominal SAPIEN size 23mm &, 26mm	The SAPIEN valve offers acceptable hydrodynamics with regurgitant fractions that were lower than those required by the ISO 5840:2005 acceptance criteria.
Flow Visualization	To qualitatively investigate flow characteristics in the vicinity of the valve.	Nominal Test: Size 23mm & 26mm Reference: Size 23mm & 27mm Irregular Test: Irregular SAPIEN size 23mm & 26mm Reference: Nominal SAPIEN size 23mm &, 26mm	The SAPIEN valve offers acceptable aortic flow patterns throughout the entire cardiac cycle. Broad central jet-like flows and no flow stasis during opening were observed in all SAPIEN valves, with no retrograde jet-like flow.

Table 5: Hydrodynamic Testing and Results			
Test	**Purpose/Objective**	**Test/Reference Articles**	**Results**
Verification of Bernoulli Relationship	To determine whether the Bernoulli relationship applies to clinical pressure drop measurements.	Nominal Test: Size 23mm & 26mm Reference: Size 23mm & 27mm Irregular Test: Irregular SAPIEN size 23mm & 26mm Reference: Nominal SAPIEN size 23mm &, 26mm	Pressure drop results for the SAPIEN valve demonstrated correlation with the Bernoulli relationship.

SAPIEN Valve Structural Performance

In vitro structural performance studies of the SAPIEN Model 9000TFX were performed. Commercially available aortic valve replacements and Cordis Palmaz Genesis stents were used as control articles in studies requiring concurrent testing of devices marketed in the U.S. A matrix of tests performed and corresponding results are provided in Table 6.

Table 6: Structural Performance Evaluation			
Test	**Purpose/Objective**	**Test/Reference Articles**	**Results**
Accelerated Wear	To assess long-term performance of the valve though accelerated wear.	Nominal Test: Size 23mm & 26mm Reference: Size 23mm & 27mm Irregular Test: Irregular SAPIEN size 23mm & 26mm Reference: Nominal SAPIEN size 23mm &, 26mm	All valves survived durability testing to 200 million cycles in accelerated wear testers without excessive structural damage and/or functional impairment. After testing to 200 million cycles, all valves met the minimum EOA and Total Regurgitation Fraction requirements of ISO 5840:2005.
Dynamic Failure Mode	To obtain information about the failure modes affecting the durability of the valve.	Test: Size 23mm & 26mm Reference: Size 23mm & 27mm	All of the failures for both the test and reference valves occurred at pressures well beyond what would be experienced *in vivo*.
Frame Crush Resistance	To evaluate the resistance of the valve to lateral compressive loads.	SAPIEN frames size 23mm, SAPIEN frames size 26mm	Minimum force required to compress the frame was acceptable.
Frame Corrosion Resistance	To characterize the corrosion resistance of the valve frames and 5-hole bars in accordance with ASTMF2129-08	Test: SAPIEN frames size 23mm, SAPIEN frames size 26mm, SAPIEN 5-hole bars Reference: Cordis Palmaz Genesis stents	Corrosion resistance of SAPIEN frames and 5-Hole Bars are equivalent to the commercially available stent.

Table 6: Structural Performance Evaluation			
Test	Purpose/Objective	Test/Reference Articles	Results
Frame Fatigue	To determine frame fatigue resistance to 600 million cycles.	SAPIEN frames size 23mm, SAPIEN frames size 26mm	No frame cracks or fractures observed at completion of 600 million cycles under 60x magnification.
Stress Analysis (FEA)	To characterize mechanical behavior of the frame during deployment and operation.	Modeling based on *in vitro* and clinical data of 23mm and 26mm SAPIEN frames.	Results indicate that the worst-case 26mm SAPIEN frame should not fracture for 600 million cycles, even under the unlikely simultaneous combination of all the worst-case conditions.

The following additional structural performance studies were completed with acceptable results: grain structure analysis, open circuit potential, material mechanical properties, fatigue life determination (i.e., Goodman diagram), force on commissure.

SAPIEN Valve Design Specific Performance Studies

Design specific in vitro performance studies of the SAPIEN Model 9000TFX were completed. The following studies were completed with acceptable results: percent surface area, frame overexpansion safety factor investigation, frame foreshortening and recoil, frame radial strength, valve migration force, pulsatile flow migration, radiopacity.

SAPIEN Valve Magnetic Resonance Imaging (MRI) Compatibility

Testing of this device in magnetic fields of 1.5 and 3.0 Tesla has shown that this device is MR Conditional. It can be scanned safely under the following conditions:

- • Static magnetic field of 1.5 Tesla or 3 Tesla
- • Spatial gradient field of 2500 Gauss/cm or less.
- • Maximum whole-body-averaged specific absorption rate (SAR) of 2 W/kg for 15 minutes of scanning.
- • Normal mode operation, as defined in IEC 60601-2-33, of the MR system.

Delivery System and Accessory Performance Testing

The following tests were performed for the RetroFlex 3 Delivery System and showed acceptable results: dimensional verification, visual inspection, simulated use, balloon characterization, bond strength, hemostasis, and migration.

The following tests were performed for the RetroFlex Balloon Catheter and showed acceptable results: dimensional verification, visual inspection, simulated use, balloon characterization, bond strength, and balloon compliance.

The following tests were performed for the Crimper and showed acceptable results: dimensional verification, visual inspection, and simulated use.

B. SAPIEN Valve Animal Studies

Feasibility studies were conducted in over 100 animals (porcine, bovine, canine, and ovine) in an attempt to identify a suitable animal model and study feasibility of percutaneous delivery of the valve. The valves used in these studies were either early prototypes (equine

and bovine) or the Cribier-Edwards™ Aortic Bioprosthesis, Model 9000. A chronic study was performed on this model of the valve in which 19 juvenile sheep with induced aortic insufficiency were treated. Fourteen (14) percutaneous implants of the 23mm Model 9000 valve were attempted in the proximal descending aorta and 5 sheep were treated surgically with the control article, a commercially available pericardial bioprosthesis. An overview of this study is provided in Table 7.

Table 7: GLP Chronic Study Overview	
Sample Size/Animal Model	19 sheep with induced aortic insufficiency (Hufnagel Model)
Test Articles	Cribier-Edwards™ Aortic Bioprosthesis, Model 9000
Control Articles	Commercially available pericardial bioprosthesis
Technique	Percutaneous implant of valve and surgical implantation of control articles in the proximal descending aorta.
Results	14 percutaneous implants attempted 10 successful animals (sacrificed between 10 - 21 weeks) 3 procedure related deaths 1 non-related early death 5 surgical implants – Control 3 procedural deaths 2 sacrificed within 48 hours due to valve issues
Conclusion	6 animals survived to 21 weeks. The gross findings and histopathology results suggest that the valve is capable of long-term implant.

A chronic *in vivo* animal implantation study was conducted using the SAPIEN Valve, Model 9000TFX in the adult ovine model. A total of eighteen test article Model 9000TFX valves were implanted in the aortic position of 18 adult male sheep for a 10 week (n=9) and 20 week (n=9) evaluation study; 3 of 9 animals survived to at least 10 weeks and 6 of 9 survived to at least 20 weeks. Three (3) control articles were implanted in the aortic position of 3 adult male sheep; 2 control animals survived to at least 20 weeks and were clinically normal prior to explant; 1 animal survived to less than 14 days. No control valves were evaluated at 10 weeks. The results of this study indicate that the 9000TFX valve model has acceptable hemodynamic performance. Normal healing with pliable leaflets and no thrombus were observed, with no evidence of infection or calcification when implanted for 20 weeks. The two valve models were comparable for all parameters evaluated. A summary of the study results is provided in Table 8.

Table 8: GLP Chronic Study Summary	
Evaluation Parameter	**Summary of Results**
Clinical History and Hematology	All 10-week and six 20-week sheep were clinically normal prior to explants. At implant and explant, hematology was within normal limits for both groups. Clinical chemistry and complete blood count results were within normal limits for the majority of animals. Among the remaining animals, some values were either slightly above or below the reported normal range but none was considered to be clinically significant. Findings were comparable between both groups. Three test animals had elevated plasma free hemoglobin; this may have been due to red cell damage during sample collection as no clinical signs of hemolysis were observed.
Hemodynamic	At 20 weeks, there were no differences from the average pre-explant peak gradients

Table 8: GLP Chronic Study Summary	
Performance	between the two groups for both normotensive and hypertensive readings, and no differences from the average post-implant and pre-explant cardiac outputs between the two groups. The six 20-week test valves had evidence of mild to moderate aortic valve insufficiency by echocardiography exams of paravalvular origin. One of two control valves had mild insufficiency. Angiography evaluation at 20 weeks indicated that 4 of 6 test valves had Grade 1-2 regurgitation of undetermined origin. Two test valves had Grade 3-4 regurgitation with at least one for paravalvular origin. One control valve had Grade 3-4 regurgitation from undetermined location.
Histopathology	Histopathology results showed no apparent differences in tissue reactions (general healing, calcification, or morphology of the tissue/valve interface) between the test device and the control device. Tissue reactions towards the test and control devices were generally of low severity and were considered to be typical of this type of device implant.
Gross Observations	General healing results were comparable among the two valve models at 20 weeks. There were no differences between the gross observation valve findings for calcific deposits, thrombus formation, vegetative growths, leaflet damage, material wear, suture integrity, right dehiscence or frame fracture. Both groups presented with minimal to moderate valve leaflet host tissue overgrowth. Individual sheep from the test group had minimal leaflet retraction and minimal to moderate paravalvular spaces was observed for both groups.

C. Sterilization

The SAPIEN Valve Model 9000TFX is sterilized by terminal liquid sterilization (TLS) in buffered glutaraldehyde solution. The RetroFlex 3 Delivery System, RetroFlex Balloon Catheter, and Crimper are sterilized by ethylene oxide (EO). After sterilization, the devices are held in quarantine until sterility is verified per process specifications. The TLS and EO processes have demonstrated Sterility Assurance Levels (SAL) exceeding the industry standard of 10^{-6} in validation studies.

D. Shelf Life

Packaging and product integrity studies were conducted to ensure that the shelf life for each package and product is maintained for a minimum of two (2) years for the SAPIEN Valve, RetroFlex 3 Delivery System, RetroFlex Balloon Catheter, and Crimper.

E. Package Integrity

The packaging for the SAPIEN valve consists of a 3.8 oz jar, a lid and gasket closure system, and shelf and shipping containers. This system has been evaluated via physical testing and microbial challenge and was shown to maintain its sterile barrier following four years of real-time aging and exposure to temperature variations and simulated shipping conditions.

The RetroFlex 3 Delivery System, RetroFlex Balloon Catheter, and Crimper are packaged in Tyvek pouches and shelf and shipping cartons. These systems have been evaluated and

shown to maintain sterile barrier following two years of accelerated aging and exposure to temperature variations and simulated shipping conditions.

F. Product Integrity

SAPIEN Valve Biological Tissue

Edwards ThermaFix-processed bovine pericardial tissue has previously been validated and approved under PMA application P860057 regarding the Carpentier-Edwards® PERIMOUNT® Pericardial Bioprosthesis product family. The tissue used for the SAPIEN valve is identical to the tissue used on the PERIMOUNT valve. Biochemical evaluation was conducted on tissue stored in glutaraldehyde solution for four years real time. All device specifications were met for moisture content, ninhydrin content, shrinkage temperature, and enzymatic digestion of tissue.

Histological examination of leaflets was conducted on leaflet samples from whole valves at zero-time and after two years of real-time aging. Results demonstrated that aging of tissue does not appear to impact the microstructure of bovine pericardial tissue used in the SAPIEN valve. A stress relaxation study was completed to compare cyclic load decay for tissue leaflet samples at zero-time to tissue leaflets at zero-time and after three years of real-time aging. No statistically significant difference was observed between groups.

SAPIEN Valve Nonbiological Components and Whole Valve Testing

Functionality of the SAPIEN valve's non-biologic components (polymers: valve holder, skirt, sleeve, and sutures; and metallics: frame and frame samples) and whole-valve hydrodynamic and wear testing were completed after 2 years real-time aging.

Tensile testing of the frame met acceptance criteria. Corrosion resistance of the frame demonstrated higher resistance than the zero-time reference. Tensile testing of all polymer components met acceptance criteria relative to zero-time reference strengths. All valves passed the minimum hydrodynamic performance requirements for EOA and Regurgitant Fraction per ISO 5840:2005. The 2 year real-time aged SAPIEN valves survived durability testing out to 200 million cycles in accelerated wear testers under aortic pressure test conditions without failure, significant tissue wear or frame deformation and fracture. These valves offered a larger EOA and lower regurgitant fractions than those required per the minimum performance requirements of ISO 5840:2005 after 200 million cycles.

Delivery System and Accessories

Functionality and product integrity of the RetroFlex 3 Delivery System, RetroFlex Balloon Catheter, and Crimper was demonstrated after following two years of accelerated aging and exposure to temperature variations and simulated shipping conditions.

X. SUMMARY OF PRIMARY CLINICAL STUDY

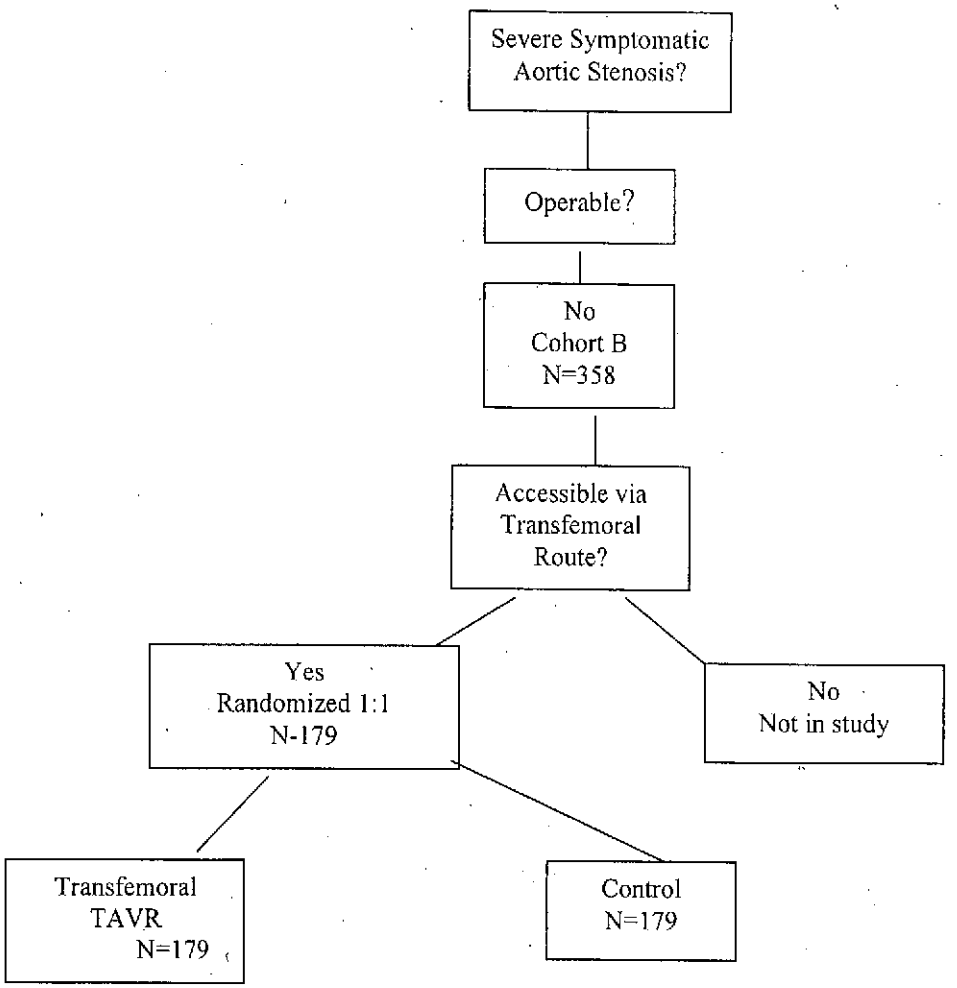
The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of transcatheter aortic valve replacement with the SAPIEN Transcatheter Heart Valve for transfemoral delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis in the U.S., Canada and Germany under IDE # G030069. 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

There were two feasibility studies conducted prior to the PARTNER pivotal study: one (REVIVAL I) involved only 5 subjects enrolled beginning January, 2005, and was terminated due to serious adverse events (three expired, two valves migrated, and there was one stroke). After assessment of the root cause of the events, the device and study designs were modified and a training program was implemented, and the second feasibility study (REVIVAL II) was begun in December, 2005. The first study used only the antegrade method of implantation; the second used the retrograde (transfemoral) approach, and involved a total of 55 retrograde procedures. Later, another 40 cases of transapical placement were added. Because these feasibility studies were performed to refine the design of the device and the pivotal study, the results are not provided in this summary, and focus is on the pivotal study.

The PARTNER pivotal trial was a prospective, unblinded, randomized, controlled, multi-center pivotal trial evaluating the safety and effectiveness of the Edwards SAPIEN THV, via transfemoral delivery, in a stratified population of inoperable patients (called the Cohort B study). Once the patient was identified as being inoperable, a determination of vascular access for transfemoral delivery was made. Those patients who were considered non-surgical candidates were stratified into Cohort B and randomized to treatment (transfemoral AVR) or control (optimal medical therapy). Those assigned to Cohort B who did not meet the criteria for transfemoral delivery were not enrolled in the study because the sponsor declined to have a transapical arm in Cohort B.

Figure 5 PARTNER Cohort B Trial Enrollment Diagram



A total of 358 patients were enrolled at a total of 27 investigational sites in Cohort B (transfemoral insertion of the SAPIEN versus "standard" therapy). Patients were randomized into the study from May 11, 2007 through arch 16, 2009. The database for this PMA reflected data collected through November 1, 2010 (with an additional update of the adverse events to June 11, 2011). Follow-up periods were discharge or 7 days, whichever comes first, 30 days, 6 months, 12 months, and annually thereafter to a minimum of 5 years post procedure, and patients were followed for a minimum of 12 months prior to submission of the PMA. Contractors were utilized for monitoring and analysis of data for several aspects of the study, including: an independent Data safety Monitoring Board (DSMB) that could contract an independent statistician; a Clinical Endpoint Committee (CEC) that was responsible for adjudicating adverse events, based on blinded data, an echocardiography core laboratory; an ECG core laboratory; an independent histopathology laboratory; and an economics quality of life core laboratory.

B. Patient Selection Process and Enrollment Criteria

Because of limitations in existing tools such as the Society of Thoracic Surgeons (STS) risk calculator, these tools were deemed inappropriate as stand-alone mechanisms for clearly identifying the "inoperable" patient. Therefore, a minimum of two surgeons and a cardiologist were required to make the initial inoperable decision, taking into account risk

factors not covered by the STS risk calculator. This decision was then reviewed by a central study committee.

The inclusion and exclusion criteria for the Cohort B study are summarized below.

Inclusion Criteria

- Patient has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s or an initial aortic valve area (AVA) of < 0.8 cm^2 (indexed effective orifice area [EOA] < 0.5 cm^2/m^2). (Qualifying AVA baseline measurement must be within 45 days prior to randomization).
- Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater.
- The subject, after formal consults by a cardiologist and two cardiovascular surgeons agree that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity should exceed 50%. The surgeons' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in these patients.

Exclusion Criteria

- Evidence of an acute myocardial infarction </= 1 month before the intended treatment (defined as: Q wave MI, or non-Q wave MI using the World Health Organization (WHO) definition).
- Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified.
- Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
- Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure, (or 6 months if the procedure was a drug eluting coronary stent implantation).
- Pre-existing prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification (MAC), severe (greater than 3+) mitral insufficiency, or Gorelin syndrome.
- Blood dyscrasias as defined: leukopenia (WBC<3000/mm^3), acute anemia (Hb< 9 mg%), thrombocytopenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy.
- Untreated clinically significant coronary artery disease requiring revascularization.
- Hemodynamic instability requiring inotropic support or mechanical heart assistance.

- Need for emergency surgery for any reason.
- Hypertrophic cardiomyopathy with or without obstruction (HOCM).
- Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) <20.
- Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
- Active peptic ulcer or upper GI bleeding within the prior 3 months.
- A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately premedicated.
- Native aortic annulus size < 18mm or > 25mm as measured by echocardiogram.
- Patient has been offered surgery but has refused surgery.
- Recent (within 6 months) cerebrovascular accident (CVA) or a transient ischemic attack (TIA).
- Renal insufficiency (creatinine > 3.0) and/or end stage renal disease requiring chronic dialysis.
- Life expectancy < 12 months due to non-cardiac co-morbid conditions.
- Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta (applicable for transfemoral patients only).
- Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe obstructive calcification, severe tortuosity or vessels size less than 7 mm in diameter (applicable for transfemoral patients only).
- Currently participating in an investigational drug or another device study. [Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials].
- Active bacterial endocarditis or other active infections.
- Bulky calcified aortic valve leaflets in close proximity to coronary ostia.

There was not a specific exclusion criterion for patients with critical aortic stenosis who had co-morbid conditions limiting the length or quality of their life.

C. Accountability of PMA Cohort

At the time of the database lock, of 358 patient enrolled in the PMA study, 124 patient in the test group and 86 patients in the control group were available for analysis at the 1 year time point (92 test subjects and 42 control subjects were available at the two year time point). The table below depicts the accountability at each follow-up period for the intent-to-treat population.

Table 9: Patient Accountability			
Follow-Up Period	Variable	ITT Test group (N=179)	ITT Control Group (N=179)
30 day	Number eligible	167	174
	Number crossover	0	0
	Number withdrew	0	1
	Number not yet due for follow-up	2	0
	Number died before visit	10	4
	Visit compliance	166 (99.4%)	165 (94.8%)
6 month	Number eligible	138	121
	Number crossover	0	0
	Number withdrew	0	5
	Number not yet due for follow-up	0	0
	Number died before visit	41	53
	Visit compliance	134 (97.1%)	119 (98.3%)
1 Year	Number eligible	124	86
	Number crossover	0	0
	Number withdrew	0	5
	Number not yet due for follow-up	0	0
	Number died before visit	55	88
	Visit compliance	123 (99.2%)	85 (98.8%)
2 Years	Number eligible	94	42
	Number crossover	0	9
	Number withdrew	0	5
	Number not yet due for follow-up	10	5
	Number died before visit	75	118
	Visit compliance	93 (98.9%)	40 (95.2%)

Study Endpoints

Primary Safety and Effectiveness Endpoints

There were two co-primary endpoints in this study:

1. Freedom from death, over the duration of the trial (superiority)
   A log-rank test p-value is reported by the sponsor. The hypotheses corresponding to the log-rank test are as follows:
   H_0: Survival function of SAPIEN = Survival function of Control
   H_1: Survival function of SAPIEN ≠ Survival function of Control.

2. Hierarchical composite of death and recurrent hospitalization (superiority)
The Finkelstein-Schoenfeld method[1] was used for the analysis of this endpoint. The hypotheses corresponding to the Finkelstein-Schoenfeld method are:

H_0: Neither survival nor the re-hospitalization is different between SAPIEN and Control arm;
H_1: At least one and possibly both are different between SAPIEN and Control arm.

The trial was designed to demonstrate superiority of the SAPIEN device to "standard" therapy (see discussion below regarding various treatments received by the control group) for either of the co-primary endpoints.

To control the type I error rate at the 0.05-level for the trial, multiplicity was handled by the Hochberg method. Applying the Hochberg method in this particular case, the Cohort B study would be deemed a success if both of the co-primary endpoints favored SAPIEN with a p-value of less than 0.05. Alternatively, the Cohort B study would also be successful if either of the co-primary endpoints were met with a p-value of less than 0.025.

Secondary Safety and Effectiveness Endpoints

This study included a number of secondary safety and effectiveness endpoints. This summary will provide details regarding the endpoints that FDA believes are most critical to the evaluation of safety and effectiveness for this device.

Key secondary safety endpoints included the following:

- Time from randomization to the first occurrence of a Major Adverse Cardiac and Cerebrovascular Event (MACCE) within 1 year. The MACCE definition included:
  - Death
  - Myocardial infarction (MI)
  - **All** stroke
  - Renal failure
- Serious Adverse Events
  - Deaths
  - Neurological Events (Stroke and Transient Ischemic Attack (TIA))
  - Aortic Insufficiency/Paravalvular Leak
  - Bleeding Event/Hemorrhage/Vascular Complications
  - Aortic Valve Regurgitation
  - Myocardial Infarction
  - Renal failure (patient requires chronic dialysis for greater than 30 days) or Renal Insufficiency (creatinine >3.5)
  - Endocarditis
  - Cardiac Re-intervention
  - Bradyarrhythmic Event
  - Mitral valve compromise

Key secondary effectiveness endpoints included the following:

- Hospitalization
  - Total hospital days through one year
  - Days alive out of the hospital through 1 year
- NYHA functional classification
- 6-Minute Walk Test
- Effective Orifice Area Responder Analysis

D. Limitations of Interpretation of Study Results

Analysis Populations

The sponsor has analyzed the study results based on two populations: Intent-To-Treat (ITT) and As Treated (AT). Of the 358 patients in the inoperable cohort, 179 were randomized to SAPIEN and 179 randomized to Control, forming the ITT population. The As Treated (AT) population was based on the treatment actually received. Therefore, the As Treated population is defined as follows:

- AT SAPIEN: Randomized Treatment patients for whom the study valve implant procedure is begun, defined as the time the study catheter is placed in the patient in the catheterization laboratory.
- AT Control: Randomized Control patients as well as patients randomized to the SAPIEN arm who did not receive a valve implant.

NOTE: The AT Control group does not include randomized Treatment patients who received open surgery in lieu of the SAPIEN.

The analyses of the primary and secondary endpoints based on the ITT population, which was pre-specified in the protocol, will be presented.

Heterogeneity of the Control Group

The majority (78.2%) of the control patients received balloon aortic valvuloplasty (BAV); 2/3 of these were within 30 days of randomization and 20% underwent repeat BAV. Others received open surgical replacement, apico-aortic conduits, transcatheter valve replacement outside of the U.S. or medical therapy.

Adverse Event Definitions

All safety analyses presented in this summary rely on the pre-specified adverse event definitions, which are included in the pertinent adverse event section of this summary.

E. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an aortic stenosis valve replacement study performed in the U.S.

Table 10: Patient Demographic Data Summary

Characteristic	Test (SAPIEN) N=179	Control N=179	*P*-value[a]
Age (yr), mean±SD	83.1±8.6	83.2±8.3	0.95
Male sex, n (%)	82 (45.8)	84 (46.9)	0.92
STS score[b], mean±SD	11.2±5.8	11.9±4.8	0.21
NYHA class, n (%):			0.68
II	14 (7.8)	11 (6.1)	
III or IV	165 (92.2)	168 (93.9)	
Coronary artery disease, n (%)	121 (67.6)	133 (74.3)	0.2
Previous myocardial infarction, n/total n (%)	33/177 (18.6)	47/179 (26.3)	0.10
Previous intervention, n/total n (%)			
CABG	58/179 (32.4)	73/179 (40.8)	0.12
PCI (percutaneous coronary intervention)	47/179 (26.3)	39/179 (21.8)	0.39
Balloon aortic valvuloplasty	25/154 (16.2)	39/160 (24.4)	0.09
Cerebral vascular disease, n/total n (%)	48/175 (27.4)	46/171 (26.9)	1.00
Peripheral vascular disease, n/total n (%)	55/178 (30.9)	45/179 (25.1)	0.24
COPD (chronic obstructive pulmonary disease), n (%):			
Any	74 (41.3)	94 (52.5)	0.04
Oxygen-dependent	38 (21.2)	46 (25.7)	0.38
Creatinine >2 mg/dl (177 µmol/liter), n/total n (%)	8/179 (4.5)	16/178 (9.0)	0.10
Atrial fibrillation, n/total n (%)	28/85 (32.9)	39/80 (48.8)	0.04
Permanent pacemaker, n/total n (%)	35/179 (19.6)	31/179 (17.3)	0.68
Pulmonary hypertension, n/total n (%)	50/118 (42.4)	53/121 (43.8)	0.9
Extensively calcified aorta, n (%)	34 (19.0)	20 (11.2)	0.05
Deleterious effects of chest-wall irradiation, n (%)	16 (8.9)	15 (8.4)	1
Chest-wall deformity, n (%)	15 (8.4)	9 (5.0)	0.29

Sixteen percent of the SAPIEN patients had a previous BAV before enrollment compared to 24% of the control patients. The control group had numerically higher percentages of patients with the following significant risk factors: coronary artery disease, previous MI, previous CABG, COPD, O2 dependence, elevated creatinine, and atrial fibrillation. The SAPIEN group had numerically higher percentages for the following significant risk factors: peripheral vascular disease, extensively calcified aorta, and chest wall deformity. Note that, although the mean age was 83, there were some relatively young patients included (e.g. 46 year old). Although not presented in the above table, FDA also notes that these patients were generally large (BSA 1.79) and Caucasian (91.3%). There was an equal distribution of males and females in the study.

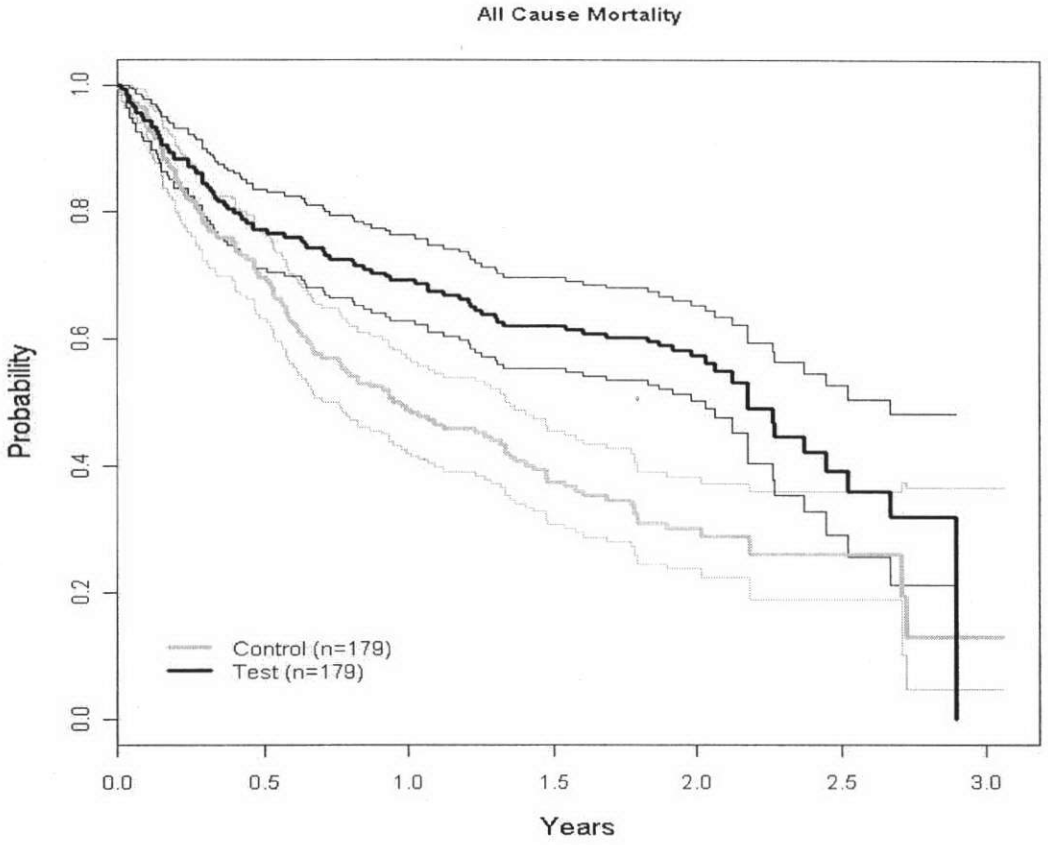
F. Primary and Co-Primary Safety and Effectiveness Endpoints and Results

Primary Safety and Effectiveness Endpoint

Freedom from death over the duration of the trial

The primary analysis was a comparison of survival through the full duration of the study. The figure below shows the mortality results in Cohort B for the ITT population, including confidence limits for each curve. All-cause mortality risk over the full duration of the study was significantly less for those assigned to SAPIEN compared to Control (p-value < 0.0001 from 2-sided log-rank test). The survival rate at one year is 69.3% and 50.3% for SAPIEN and Control, respectively.

Figure 6



Number at Risk						
Test	**179**	**138**	**124**	**103**	**61**	**130**
Control	**179**	**122**	**85**	**56**	**24**	**41**

There was a reduction in mortality with this device relative to the heterogenous control group, and the endpoint was met. There are limited data beyond 2 years from the PARTNER trial and the long-term mortality benefit of the SAPIEN THV is unknown.

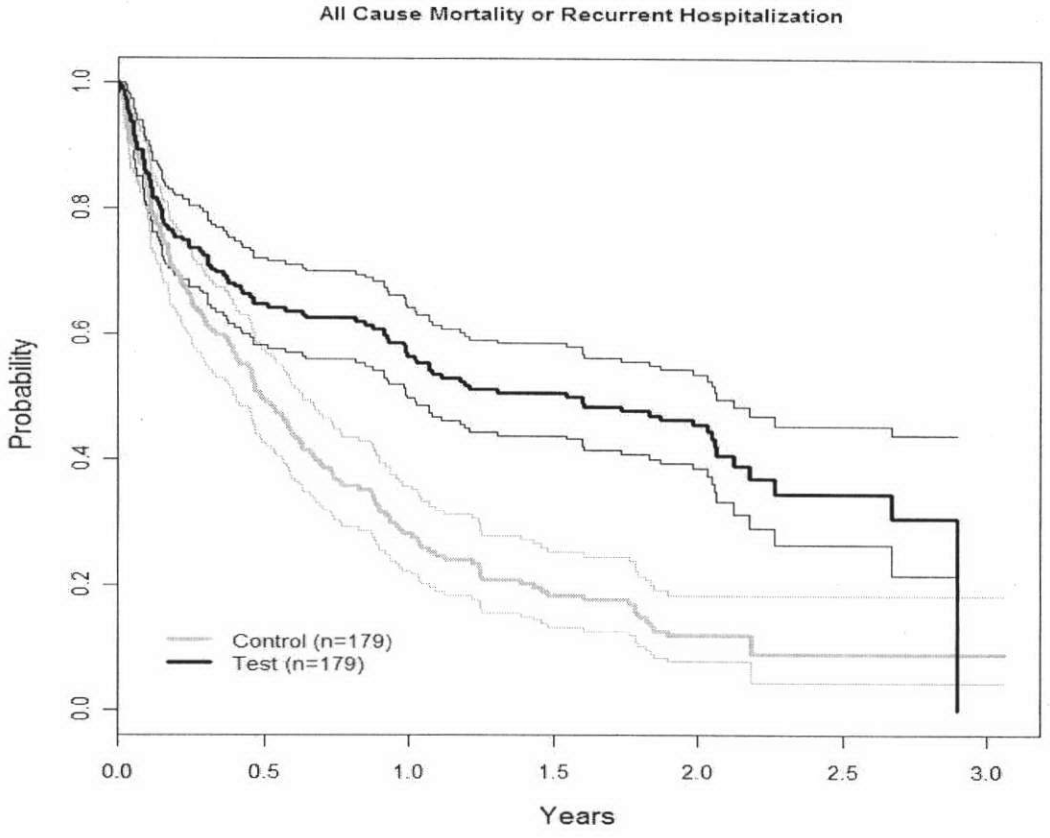
Co-Primary Safety and Effectiveness Endpoint

Hierarchical composite of death and recurrent hospitalization

The additional co-primary endpoint was defined as a hierarchical analysis of the time from randomization to death from any cause or to the first occurrence of recurrent hospitalization, which was analyzed according to the Finkelstein-Schoenfeld method. The analysis was statistically significant (p-value <0.0001 from 2-sided Finkelstein-Schoenfeld test) in favor of the SAPIEN group.

The Kaplan-Meier survival curve is below, including confidence limits. This endpoint also shows a clinically important difference between arms of this trial over the first two years of follow-up.

Figure 7



Number at Risk					
Test	**179**	**116**	**101**	**85**	**49**
Control	**179**	**87**	**49**	**29**	**10**

G. Secondary Safety Endpoints

Major Adverse Cardiac and Cerebrovascular Events (MACCE)

Time from randomization to the first occurrence of a MACCE event within 1 year

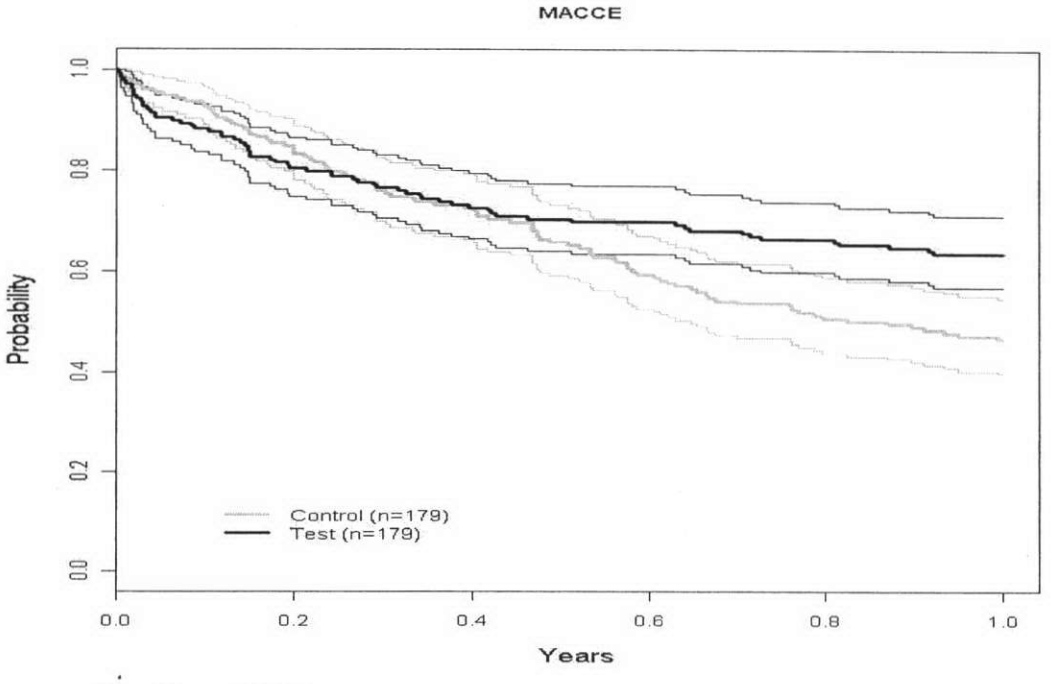
For the purposes of this analysis, MACCE includes all-cause death, myocardial infarction (MI), all stroke, and renal failure. The comparison was performed by the log-rank test and a two-sided p-value was reported. All data were truncated at one year for the analysis; patients alive and MACCE free at that time point were censored. The log-rank test favors the SAPIEN arm with p-value 0.0176.

Table 11: MACCE Summary Table				
	30 Days		1 Year	
	Test (SAPIEN) (N = 179)	**Control** (N = 179)	**Test (SAPIEN)** (N = 179)	**Control** (N = 179)
Outcome	*no. of patients (%)*		*no. of patients (%)*	
Death (all cause)	9 (5.0)	5 (2.8)	55 (30.7)	89 (49.7)
Stroke	13 (7.3)	3 (1.7)	20 (11.2)	8 (4.5)
Myocardial Infarction (MI)	0	0	1 (0.6)	1 (0.6)
Renal failure	2 (1.1)	2 (1.1)	4 (2.2)	5 (2.8)

The above table shows that there were minimal differences in MI and renal failure. The early stroke rate was 4.3 times higher in the SAPIEN group and the 1 year stroke rate was 2.5 times higher than the control group, who were primarily treated with BAV. Death is counted as a component of the primary endpoints as well as the MACCE, thus resulting in double counting of this component.

The figure below presents the cumulative MACCE rate over the first year of follow-up. In both the table and figure, the SAPIEN had a higher incidence of events <30 days, but lower incidence of death after 30 days.

Figure 8



Number at Risk

Test	**179**	**144**	**130**	**125**	**119**
Control	**179**	**149**	**128**	**103**	**81**

Serious Adverse Events that Occurred in the PMA Clinical Study

The following is a summary of the Serious Adverse Events (SAEs) that occurred in this study:

Table 12: Clinical Outcomes at 30 Days and 1 Year						
	30 Days			1 Year		
	Test (SAPIEN) (N = 179)	**Standard Therapy** (N = 179)	P Value†	**Test (SAPIEN)** (N = 179)	**Standard Therapy** (N = 179)	P Value†
Outcome	*no. of patients (%)*			*no. of patients (%)*		
Death						
From any cause	9 (5.0)	5 (2.8)	0.41	55 (30.7)	89 (49.7)	<0.001
From cardiovascular cause‡	8 (4.5)	3 (1.7)	0.22	35 (19.6)	75 (41.9)	<0.001
Repeat hospitalization∫	10 (5.6)	18 (10.1)	0.17	40 (22.3)	79 (44.1)	<0.001
Death from any cause or repeat hospitalization∫	20 (11.2)	22 (12.3)	0.74	78 (43.6)	126 (70.4)	<0.001
Stroke◊	13 (7.3)	3 (1.7)	0.02	20 (11.2)	8 (4.5)	0.03
Transient Ischemic Attack	0	0	1	1 (0.6)	0	1
Myocardial infarction						
All	0	0	-	1 (0.6)	1 (0.6)	1
Periprocedural	0	0	-	0	0	-
Hemorrhagic Vascular Complication	90 (50.7)	25 (14.0)	<0.0001	100(55.9)	25(14.0)	<0.0001
Renal failure	2 (1.1)	2 (1.1)	1	4 (2.2)	5 (2.8)	0.59
Renal Insufficiency‡	1 (0.6)	0 (0.0)	1	2 (1.1)	3 (1.7)	1
Bleeding Event	29 (16.2)	4(2.2)	<0.0001	31(7.3)	4(2.2)	<0.0001
Cardiac re-intervention						
Balloon aortic valvuloplasty	1 (0.6)**	2 (1.1)	1	1 (0.6)	66 (36.9)‡‡	<0.001
Repeat TAVR‡‡	3 (1.7)	NA	-	3 (1.7)	NA	-
Aortic-valve replacement	0	3 (1.7)	0.25	2 (1.1)**	17 (9.5)	<0.001
Endocarditis	0	0	-	2 (1.1)	1 (0.6)	0.31
New atrial fibrillation	1 (0.6)	2 (1.1)	1	1 (0.6)	3 (1.7)	0.62
New pacemaker	6 (3.4)	9 (5.0)	0.6	8 (4.5)	14 (7.8)	0.27

* NA denotes not applicable.

† P values are for between-group comparisons of the frequency of the event at each time point, using Fisher's exact test.

‡ Deaths from unknown causes were assumed to be deaths from cardiovascular causes.

∫ Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR). Patients who received renal-replacement therapy were not included.

‖ Patients who received renal-replacement therapy after randomization were included.

** One patient in the TAVR group did not receive TAVR (because of failed access) and subsequently underwent BAV, followed by aortic-valve replacement.

†† A total of 30 patients underwent a repeat BAV after the index balloon aortic valvuloplasty procedure that had been performed in the first 30 days after randomization, and 36 patients underwent a first BAV more than 30 days after randomization.

‡‡ Three patients underwent a repeat TAVR within 24 hours after the index TAVR procedure; four patients in the standard-therapy group who underwent TAVR at a nonparticipating site outside the United States are not included here.

◊ Stroke defined using pre-specified definition of deficit lasting >/= 24 hours or less than 24 hours with a brain imaging study showing an infarction

Neurological Events

The pre-specified definition of stroke was as follows:

Stroke: A neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction

All Neurological Events at 30 Days, 1 Year, and Total Study (ITT Population)

Table 13: Neurological Events To One Year		
Follow-up Window	**Control # Events (% patients)**	**Test (SAPIEN) # Events (% patients)**
0-30 days	3 (1.7%)	13 (7.3%)
<5 days from SAPIEN implant		11/13
31 days – 1 year	5 (2.8%)	8 (4.5%)
> 1 year	0	4 (2.2%)
Total in study	8 (4.5%)	25 (14.0%)

This table shows that the acute neurological event risk is 4.3 times higher in the SAPIEN arm compared to Control, noting that the majority of controls had BAV. The total neurological event rate in the study was 3.1 times higher in SAPIEN than Control. Interpretation of this increased late stroke rate is complicated because of the higher mortality rate in the Control group.

The types of neurological events that occurred during the course of the study are listed in the table below:

All Neurological Events Through Duration of Study (ITT Population)

Table 14: Neurological Events Through Duration of Study		
Neurological Event	**Control**	**Test (SAPIEN)**
Ischemic/unclassified Stroke	7	16
Hemorrhagic Stroke	1	3
Intracranial Hemorrhage	0	3
TIA	0	3 (2 patients)
Total Events	8	25

Neurological Events in the Control Group

There were 7 ischemic/unclassified strokes:

- 1 after open AVR
- 4 after BAV (5 days, 2 weeks, 2 months, 6 months)
- 2 in patients who only received medical management (one on the day of randomization, and another 3 days after randomization)

There was one hemorrhagic stroke 8 months after BAV.

Only 14 control patients had optimal medical therapy without an interventional aortic valve procedure throughout the trial. As mentioned above, two of these 14 patients had strokes within 3 days of randomization, but there were no further strokes. Fourteen additional

patients had either open AVR or apico-aortic conduits. One of these 14 patients had a stroke on the day of surgery. There were no further strokes throughout the trial in the Control group. Therefore, the control group had minimal neurological events over 60 days after invasive procedures and there does not appear to be an elevated continuing risk of neurological events. As a result, there is no evidence that the patients in this study were a high risk stroke population.

Neurological Events in the SAPIEN *Group*

There were 16 ischemic/unclassified strokes:

- 1 occurred after randomization and before SAPIEN
- 10/16 were recognized within 6 days of SAPIEN implantation or attempted implantation
- 2/16 occurred from 23-180 days (23, 75 days)
- 3/16 occurred late (361, 650, 875 days)

There were 3 hemorrhagic strokes (2, 39, and 120 days); 3 intracranial hemorrhages (51, 136, 151 days); and 3 TIAs (143 days in one patient; 386 and 831 days in a second patient).

Twelve of 25 (48%) of the neurological events occurred > 30 days after the procedure – thus indicating a continued risk of neurological events with the device.

Comparing BAV (5/150; 3.3%) and SAPIEN (24/175; 13.8%), there is a higher neurological event rate in the SAPIEN patients, both in the acute peri-procedural period and during longer-term follow-up. Neurological adverse events remain an important safety consideration for this device.

Bleeding Events/Hemorrhage/Vascular Complications

The PARTNER protocol prospectively defined adverse events relating to bleeding and vascular complications as follows:

Bleeding Event: Any episode of major internal or external bleeding that causes death, hospitalization or permanent injury (e.g., vision loss) or necessitates transfusion of greater than 3 units packed red blood cells (PRBCs) or pericardiocentesis procedure. The complication bleeding event applies to all patients whether or not they are taking anticoagulants or antiplatelet drugs, since bleeding events can occur in patients who are not receiving anticoagulants. Embolic stroke complicated by bleeding is classified as a neurologic event under embolism and is not included as a separate bleeding event. Hemorrhage that requires 2 or more units of transfusion within the index procedure shall be reported as serious adverse events.

Aortic Dissection: Aortic dissection defined as Type A or B dissections that require surgical or percutaneous intervention.

Hemorrhage: See "Bleeding event"

Events which are excluded are: those due to liver disease, myocardial infarction, or systemic infection.

Bleeding events were reported as major or minor as defined below:

Major: Requires intervention.
Minor: Does not require intervention.

Hemorrhagic Vascular Complication

Vascular complications include the following:
1. Hematoma at access site >5 cm
2. False aneurysm
3. Arterio-venous fistula
4. Retroperitoneal bleeding
5. Peripheral ischemia/nerve injury
6. Any transfusion required will be reported as a vascular complication unless for a clinical indication clearly other than catheterization complication.
7. Vascular surgical repair

Half (55.9%) of the SAPIEN patients had serious adverse events relating to the access procedure. The table below lists the most serious of the vascular complications.

Table 15: Vascular Complication Summary	
Acute Vascular complication	**# patients**
Aortic dissection	1
Iliac artery/distal aortic injury	17
Femoral artery injury	13
Pseudoaneurysm	2
Hematoma	6
Unknown injury	2

Aortic Regurgitation

The table below presents the total amount of aortic regurgitation (moderate or greater) reported from the core laboratory at the listed follow-up points in both treatment arms. These totals include all sources of regurgitation, including both central regurgitation and paravalvular leak.

Table 16: Aortic Regurgitation Comparison (moderate or greater)		
Follow-up Visit	**Control (% patients)**	**Test (SAPIEN) (% patients)**
30 days	16.5%	15.2%
6 month	16.8%	9.9%
1 yr	16.7%	15.6%

These data show that the amount of aortic regurgitation (AR) does not decrease over time in the SAPIEN group. Because of the heterogeneity of treatments received in the Control group, comparison to the Control group is limited.

Endocarditis

There were no endocarditis events reported in the Control group. In the SAPIEN group, 3/175 (1.7%) patients experienced endocarditis. Two of these patients died and the third had an explant and open AVR. This explanted patient had a difficult post-SAPIEN implant course with septicemia then returned 19 months later with acute decompensation and a stenotic valve. He underwent open operation and was discharged from the hospital after a complicated course. Pathologic evaluation of the valve showed endocarditis and severe calcification of all three leaflets of the SAPIEN. These cases confirm the need for longer-term (>1-2 years) monitoring of this device in this patient group, as the patients are at risk over the life of the valve.

Aortic Valve Re-intervention

The SAPIEN group had a 2.3% incidence of this SAE while the control group had a 66.9% incidence. This reflects expected BAV in control patients. If a control patient had a BAV more than 30 days after randomization, it is counted as an aortic valve re-intervention.

Other Serious Adverse Events

Data were also collected for the following adverse events: myocardial infarction, renal failure (chronic dialysis for >30 days), renal insufficiency (creatinine >3.5), bradyarrhythmic event, and mitral valve compromise. Based on the available data, these potential procedure-related complications did not appear to be clinically significant in the context of this study.

H. Secondary Effectiveness Endpoints and Results

Key effectiveness outcomes are presented below, by category.

Hospitalization

Hospitalization for any reason is a generally accepted surrogate measure of quality of life for patients and is therefore considered an important secondary endpoint. Hospitalization was analyzed two different ways in this trial in an attempt to describe the differences between the Treatment and Control groups.

Total Hospital Days Through 1 Year

This endpoint captured the total hospital days from the index procedure (SAPIEN arm) or randomization (Control arm) to one year post-procedure or randomization. For the purposes of analyzing this endpoint, it should be noted that the hospitalization for the valve implantation procedure in the SAPIEN arm was not counted. The sponsor reported the SAPIEN and Control arm results (mean ± SD) to be 18.4±20.3 and 13.8±17.9, respectively. The bootstrap test yielded p-value of 0.019 favoring the Control arm.

Days Alive and Out of the Hospital (DAOH) Through One Year

An analysis of DAOH allows for an assessment of two important objectives of the device therapy – improvement in mortality and quality of life. Note that the index hospitalization for SAPIEN implantation was included in this analysis. The sponsor reported the SAPIEN and Control arm results to be 273.8±128.5 and 210.2±146.9, respectively. Based on the proximity of these values, no conclusions could be drawn about the treatment or control arms.

New York Heart Association Functional Class

An evaluation of cardiac symptom severity based on NYHA classification was conducted at several evaluation time points during the first year of the trial. At baseline, patients presented with the following breakdown of NYHA class:

Table 17: Baseline NYHA

Arm	NYHA at Baseline			Total
	II	III	IV	N
Control	11	87	81	179
SAPIEN	14	87	78	179
Total	25	174	159	358

At 1 year, the following results of the NYHA evaluation were reported:

Table 18: NYHA at 1 Year

Arm	PMA: NYHA at One Year						Total
	Missing	Dead	I	II	III	IV	N
Control	11	89	2	29	37	11	179
SAPIEN	7	55	45	44	23	5	179
Total	18	144	47	73	60	16	358

In the ITT population, more patients in the SAPIEN group had less severe cardiac symptoms (NYHA class I or II) as compared to patients in the Control group (49.7% vs. 17.9%, respectively). The between-group difference remained statistically significant, favoring SAPIEN, across a number of sensitivity analyses using various methods for imputing missing data other than death. Specifically, the analysis that imputes test arm NYHA missing for reasons other than death to NYHA IV, control arm with NYHA missing for reasons other than death to have NYHA I, and death to have NYHA V yields p-value 0.0005 that favors the SAPIEN arm.

Despite the statistically significant result, it is important to note the limitations of subjective measures such as NYHA in this unblinded study due to the influence of placebo/nocebo effects and assessment bias.

6-Minute Walk Test

Based on the available data from the test performed at 1 year, patients in the SAPIEN group were able to walk further during a 6-minute walk test (6MWT) than those in the Control group (mean ± SD, 118.93 + 147.3 vs. 84.40 + 96.83 meters).

The most important observation is that only 45.2% (56/124) of the alive SAPIEN patients and 34.4% (31/90) of the alive Control patients completed the 6MWT at one year. The impact of missing data is unknown and therefore limits the ability to draw conclusions regarding these results.

Effective Orifice Area (EOA) Responder Analysis

For the purpose of this analysis, a responder was defined as maintenance of >50% of the EOA at the follow-up time periods. The following results were noted for the SAPIEN group (based on the As Treated population):

Table 19: EOA (AT population)	
30 days n=133	92%
6 months n=93	85%
1 year n=82	90%

This shows that the reduction in stenosis was maintained at least at a reasonable level for the first year in the SAPIEN group.

I. Additional Study Observations

Procedure Data

The following table provides data on the transcatheter valve implantation procedure for patients in the SAPIEN arm. These data demonstrate that the procedure took, on average, over 4 hours and required general anesthesia in all patients. Also, 10% of the patients either did not get a valve or got more than one valve. There was a relatively even distribution of the two valve sizes. There is not comparable data for the control patients who underwent BAV.

Table 20: Procedural Data Summary	
Variable	Mean or % of patients (min – max)
Total time of procedure (min)	262 (139-616)
Skin to skin time (min)	150 (34 – 553)
Fluoroscopy time (min)	29 (10-68)
Volume of contrast (ml)	132 (10-450)
Use of CPB	1.1%
Use of general anesthesia	100%
# of devices used	
0	4.6%
1	89.1%
2	5.7%
3	0.6%
Valve in Valve procedure	2.3%
Emergent operation due to device or procedure	1.1%
Valve Size	
23	56.6%
26	43.4%
Adverse event during procedure	39.4%
Device malfunction	3.4%
Device Success (deployment, AVA >0.9, AI<3+, 1 valve)	78.2%

Procedure Success (Device success, no MACCE <30d)	71.8%

Valve-in-Valve Experience

Four patients underwent valve-in-valve procedures in the Cohort B study, either because of migration of the valve, or due to unacceptable regurgitation. Without any pre-clinical testing, and limited clinical data, the FDA is unable to draw conclusions regarding the short- and long-term safety of SAPIEN valve-in-valve implantation.

Patient Selection Limitations

Because there were no specific inclusion/exclusion criteria in this study to eliminate patients too sick to benefit from isolated treatment of severe aortic stenosis, there was limited, active consideration for patients who should not have transcatheter valve implantation due to extensive comorbidities. .SAPIEN implantation requires general anesthesia, 4+ hours of procedure time, radiographic contrast, invasive TEE, often an operative procedure for vascular access or closure, etc.; and therefore, it is considered to be a highly invasive interventional cardiology procedure. Although there is a mortality benefit that exists for this device in patients considered to be inoperable, the overall impact on a patient's quality of life when considering the totality of the data remains unknown due to the limitations of the available data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The sponsor estimates that 7,054 SAPIEN devices have been implanted in the commercial use of this device since October 2007, over half of whom were enrolled in some form of trial or registry. Follow-up data on these patients and clinical interpretation is limited for the reasons outlined later in this section. The mortality results are as follows:

Table 21: Summary of European Clinical Experience

Trial	Number of Subjects Enrolled	Number of Subjects Receiving Valve	Survival at 1 month %	Survival at 6 months %	Survival at one year %
I-REVIVE	22	17	67.2%	33.6%	28.0%
RECAST	24	20	72.3%	48.2%	43.4%
REVIVAL-1	7	7	57.1%	28.5%	25.5%
REVIVAL-2 Transfemoral	55	48	92.7%	83.4%	75.8%
REVIVE 2	106	94	86.8%	78.9%	72.5%
REVIVAL 2-Transapical	40	35	82.5%	65.0%	59.5%
TRAVERCE	172	169	84.7%	69.0%	62.6%
PARTNER EU Transapical	69	65	81.2%	58.0%	49.3%
PARTNER EU Transfemoral	61	65	91.8%	90.2%	78.7%
SOURCE Registry Transapical – Cohort 1	575	523	89.7%	NAP	72.1%
SOOURCE Registry Transfemoral – Cohort 1	463	443	93.7%	NAP	81.1%
SOUIRCE Registry Cohort 1	1038	966	91.2%	NAP	NAP
SOURCE Registry – Cohort 2	1306		89.9%	NAP	NAP
PARTNER IDE Cohort B Transfemoral	358 randomized	173	95.0%	NAP	69.3%
PARTNER Cohort B Standard Therapy	358 randomized	0	97.2%	NAP	49.3%
Total	4296				

Table 21: Summary of Canadian Clinical Experience					
Special Access	Number of Subjects	Number of Subjects Receiving Valve	Survival at 1 month %	Survival at 6 months %	Survival at one year %
Canada Special Access (transfemoral)	168	167	90.5%	--	75%
Canada Special Access (transapical)	177	172	88.7%	--	78%
TOTAL	345	339			
Compassionate Use	Number of Subjects	Number of Subjects Receiving Valve	Survival with valve		
I-REVIVE	6	6	0		
REVIVAL-1	1	1	1		
REVIVAL-2	2	2	2		
TOTAL	9	9	3		

The PARTNER EU trial (130 patients), and all of the registries in Europe (SOURCE Registries, n=3382), used the EuroScore risk prediction system for defining high risk and inoperability (i.e., predicted mortality >50%). The EuroScore was developed primarily using data from coronary bypass patients with a relatively small contribution from isolated aortic and mitral valve patients. Several studies have compared the STS Risk predictor score for aortic valve replacements with the EuroScore in the aortic stenosis population and have found limitations of the EuroScore in high risk patients. In this population the EuroScore can over-predicts risk by as much as a factor of three.[2,3]

As a result, the trial results in Europe are very difficult to interpret because it is unclear who the patients were who were enrolled in these registries. One can only surmise from the inclusion criteria that the European trials were not trials primarily of "inoperable" patients. For example, surgeon input as to operability was not required in these trials. Other significant limitations include the lack of a concurrent control or clinical plans for longer-term follow-up.

Therefore, the European experience alone does not answer the longer-tern durability and outcomes questions that the pivotal study was able to answer for this patient population.

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

A. Panel Meeting Recommendation

An advisory meeting of the Circulatory System Devices Panel was held on July 20, 2011, at which three questions were held for a vote. The outcome of the votes was as follows:

Question 1
The Panel voted 7 to 3 that the data does show that there is reasonable assurance that the Edwards SAPIEN™ Transcatheter Heart Valve is safe for use in patients with severe symptomatic aortic stenosis who meet the criteria specified in the proposed indication.

Question 2
The Panel voted 9 to 1 that there is reasonable assurance that the Edwards SAPIEN™ Transcatheter Heart Valve is effective for use in patients with severe symptomatic aortic stenosis who meet the criteria specified in the proposed indication.

Question 3
The Panel voted 9 to 0 (with 1 abstention) that the benefits of the Edwards SAPIEN™ Transcatheter Heart Valve for use in the indicated patient population do outweigh the risks of the Edwards SAPIEN™ Transcatheter Heart Valve for use in the indicated patient population.

The Panel further recommended refinements to the physician and patient labeling, and that a refined Post Approval Study be submitted, as follows:

(1) refinements to the indication statement in the Instructions for Use (IFU) to limit use in symptomatic patients, and in the native annulus, and inclusion of information regarding use of BAV in the control group

(2) addition of a warning statement regarding use of valve-in-valve technique

(3) refinements to the patient label, especially in the area of stroke risk

(4) protocols for two post-approval studies: one following the patients enrolled in the IDE out to 5 years, and another study in newly implanted subjects to evaluate learning curve, anticoagulation, and adverse events compared to those seen in the IDE study

B. FDA's Post-Panel Action

FDA worked interactively with the sponsor to refine the labeling and Post Approval Study protocols to meet all of the recommendations of the Panel and the FDA.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The results from the pre-clinical laboratory studies performed on the Edwards SAPIEN Transcatheter Heart Valve Model 9000TFX and accessories for biocompatibility, hydrodynamic performance, and structural integrity demonstrate that this device is suitable for long-term implant. There was a mortality benefit in this patient population, but a higher risk of stroke and vascular injury. The Panel and FDA believed that the benefits outweighed the risks in this limited patient population.

B. Effectiveness Conclusions

The preclinical data demonstrate that the valve performs acceptably. In the clinical study, there was an improvement in hemodynamic parameters (AVA and EOA), as well as subjective parameters such as the NYHA class and Quality of Life parameters evaluated.

C. Overall Conclusions

The preclinical and clinical studies submitted in the PMA application provide reasonable assurance that the Model 9000TFX, available in sizes 23 and 26mm, and accessories are safe and effective for the replacement of native aortic valves in symptomatic, inoperable patients.

XV. CDRH DECISION

FDA issued an approval order on November 2, 2011. The final conditions of approval cited in the approval order are described below.

1. *Continued Follow-up of Premarket Cohort:* This study should be conducted as per the protocol submitted as an attachment to your September 3, 2011 electronic mail message, Version 5.0. The objectives of this study are to describe the five-year durability and quality of life outcomes associated with use of the SAPIEN device. Durability will be evaluated using aortic insufficiency as measured via echocardiogram. Quality of life will be measured using the following assessments: Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQol (EQ)-5D Utilities. The surviving patients in the premarket cohort at the time of PMA approval will be followed annually up to 5-years.

2. *Newly Enrolled Study*: This study should be conducted as per the protocol submitted as an attachment to your October 18, 2011, Version 1.0. The objectives of this study are to evaluate: (1) the neurological and vascular outcomes at 30 days and annually through five years post-implant, (2) the learning curve among surgical teams placing the device at 50 geographically disbursed sites with high, moderate and low volumes of potential patient participation, and (3) composite safety and effectiveness endpoints at 30 days and annually through five years post-implant. Based on a background rate of 7.43% and censoring of 10% across the first year post-implant, it was calculated that a sample size of 1,100 patients is needed to have adequate power to assess the primary endpoint of neurological outcomes at one year post-implant. The data collection for this study (i.e. pre-procedure, peri-procedure, post-procedure, discharge, 30-day, and 1-year follow-up) must be nested within the National Transcatheter Aortic Valve Replacement (TVT) registry housed jointly by the American College of Cardiology and Society for Thoracic Surgeons within four months of its initiation. You have also agreed to link the data to Centers for Medicare and Medicaid Services (CMS) data for long-term follow-up (annually through five years post-implant).

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

XVII. APPROVAL SPECIFICATIONS

Directions for use: See final approved labeling (Instructions for Use)

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the final labeling (Instructions for Use)

Post-approval Requirements and Restrictions: See Approval Order.

XVI. REFERENCES

[1] Finkelstein D, Schoenfeld D., *Combining mortality and longitudinal measures in clinical trials.* Statistics in Medicine, 1999; 18: 1341-54.

[2] Wendt, et al. *Society of Thoracic Surgeons score is superior to the EuroScore determining mortality in high risk patients undergoing isolated aortic valve replacement.* Ann Thor Surg, 2009; 88(2): 468-74.

[3] Dewey, et al. *Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement.* J Thorac Cardiovasc Surg, 2008 Jan; 135(1): 180-7.