SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1. 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 Ascendra™ Balloon Catheter, Models 9100BCL23 and 9100BCL26 Ascendra™ Balloon Aortic Valvuloplasty Catheter, Model 9100BAVC Ascendra™ Introducer Sheath Set Model 9100IS Crimper, Models 9100CR23 and 9100CR26)
Applicant Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 9261
Date of Panel Recommendation:	June 13, 2012
PMA Application Number:	P110021
Date of FDA Notice of Approval:	October 19, 2012
Expedited:	Granted expedited review status on May 2, 2011 because the SAPIEN device represents a breakthrough technology that provides a clinically meaningful option in a high risk patient population.

The SAPIEN Transcatheter Heart Valve was previously approved for use in inoperable patients under P100041. The Summary of Safety and Effectiveness supporting the previous indication is available on the CDRH web site http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100041b.pdf. Previously, the Indication for Use (for the inoperable patient) read as follows:

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.

2. INDICATIONS FOR USE

TRANSFEMORAL PROCEDURE

The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23 mm and 26 mm, is indicated for transfemoral delivery in patients with severe symptomatic calcified native aortic valve stenosis without severe aortic insufficiency and with ejection fraction >20% who have been examined by a heart team including an experienced cardiac surgeon and a cardiologist and found to either be: 1) inoperable and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis; or 2) be operative candidates for aortic valve replacement but who have a Society of Thoracic Surgeons predicted operative risk score ≥8% or are judged by the heart team to be at a ≥15% risk of mortality for surgical aortic valve replacement.

The RetroFlex 3 Delivery System is indicated for the transfemoral delivery of the Edwards SAPIEN transcatheter heart valve.

TRANSAPICAL PROCEDURE

The Edwards SAPIEN transcatheter heart valve, model 9000TFX, sizes 23 mm and 26 mm, is indicated for transapical delivery in patients with severe symptomatic calcified native aortic valve stenosis without severe aortic insufficiency and with ejection fraction > 20% who have been examined by a heart team including an experienced cardiac surgeon and a cardiologist and found to be operative candidates for aortic valve replacement but who have a Society of Thoracic Surgeons operative risk score ≥ 8% or are judged by the heart team to be at a ≥15% risk of mortality for surgical aortic valve replacement.

The Ascendra Balloon Catheter is indicated for the transapical delivery of the Edwards SAPIEN transcatheter heart valve.

3. 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.

4. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the labeling for the SAPIEN Transcatheter Heart Valve with the Ascendra Delivery System and in the SAPIEN Transcatheter Heart Valve with the Retroflex 3 Delivery System.

5. DEVICE DESCRIPTION

5.1 SAPIEN Transcatheter Heart Valve

The Edwards SAPIEN Transcatheter Heart Valve (bioprosthesis), intended for transcatheter valve implantation (TAVI), 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.

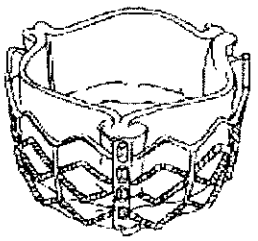

Figure 1 - Edwards SAPIEN Transcatheter Heart Valve

5.2 The RetroFlex 3 Delivery System

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.

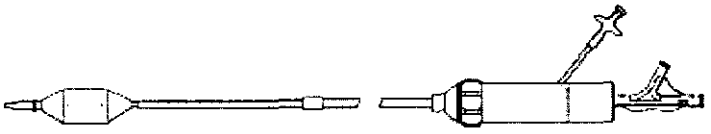

Figure 2 - RetroFlex 3 Delivery System

5.3 The RetroFlex Balloon Catheter

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.

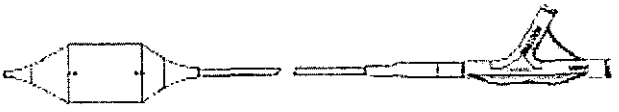

Figure 3 - RetroFlex Balloon Catheter

5.4 The Ascendra Balloon Catheter

The Ascendra Balloon Catheter, shown in Figure 4, includes a handle with deflection mechanism, a pusher tip to aid in valve placement, a balloon for deployment of the bioprosthesis, and 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. The Ascendra Balloon Catheter is supplied with a loader that covers

the crimped valve as it is inserted into the Ascendra sheath, and optional extension tubing.

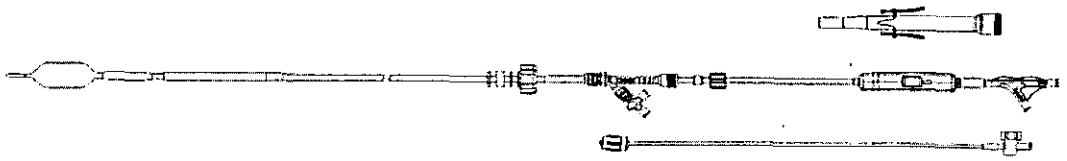

Figure 4 - Ascendra Balloon Catheter

5.5 The Ascendra Balloon Aortic Valvuloplasty Catheter

The Ascendra Balloon Aortic Valvuloplasty Catheter, shown in Figure 5, is a coaxial catheter with a distal inflatable balloon intended to pre-dilate the stenotic aortic valve prior to implantation of the bioprosthesis. Two radiopaque marker bands indicate the dilating section of the balloon and aid in balloon placement. At the proximal end of the catheter, there is a standard "Y" connector for balloon inflation and a guidewire lumen. The Ascendra Balloon Catheter is supplied with optional extension tubing.

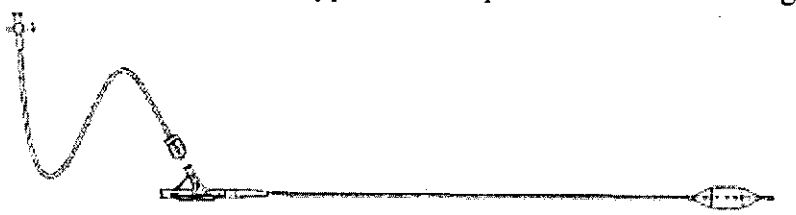

Figure 5 - Ascendra Balloon Aortic Valvuloplasty Catheter

5.6 The Ascendra Introducer Sheath Set

The Ascendra Introducer Sheath Set, shown in Figure 6, is used for the introduction and removal of devices used with the Edwards SAPIEN transcatheter heart valve. It consists of two components, sheath and introducer. The introducer is inserted in the sheath during device preparation. A radiopaque marker is located at the sheath tip for visualization when inserting the sheath. There are printed non-radiopaque depth markings on the distal end of the body that can be used to gauge the depth of distal end of the sheath within the ventricle.

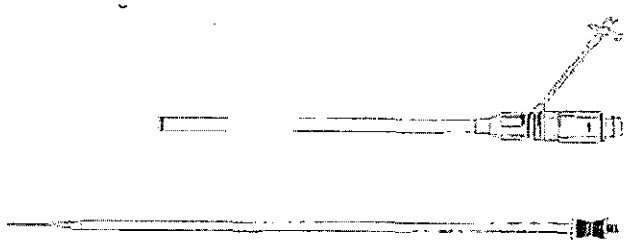

Figure 6 - Ascendra Introducer Sheath Set

5.7 The Crimper

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.

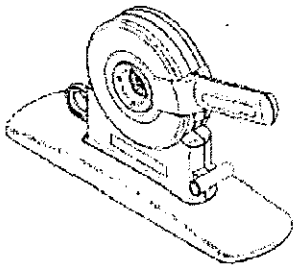

Figure 7 - Crimper

6. ALTERNATIVE PRACTICES AND PROCEDURES

Alternatives for patients with severe symptomatic native aortic valve stenosis 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). For patients who are operable, surgical aortic valve replacement (AVR) is an alternative. 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.

7. MARKETING HISTORY

Commercial distribution of the SAPIEN Transcatheter heart valve Model 9000TFX and accessories outside the United States (U.S.) began in October 2007. The SAPIEN Transcatheter Heart Valve has been marketed in the U.S. for inoperable patients since November 2, 2011. 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.

8. 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

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- 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

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

- Stroke
- Vascular injury necessitating graft placement
- 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 10 below.

9. SUMMARY OF PRECLINICAL STUDIES

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.

9.1 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, Ascendra Balloon Catheter, Ascendra Introducer Sheath Set, Ascendra Balloon Aortic Valvuloplasty Catheter are provided in Table 2. Results for the Crimper are provided in Table 3. 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 Transcatheter Heart 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.

Test	Purpose	Results
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.
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 for RetroFlex 3 Delivery System, RetroFlex Balloon Catheter, Ascendra Balloon Catheter, Ascendra Balloon Aortic Valvuloplasty Catheter, and Ascendra Introducer Sheath Set

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 i*n 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 3 - Summary of Biocompatibility Testing for 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.

Test	Purpose	Results
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.

9.2 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 4.

Table 4 - 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.
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.

Test	Purpose/Objective	Test/Reference Articles	Results
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.
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.

9.3 SAPIEN Valve Structural Performance

In vitro structural performance studies of the SAPIEN Model 9000TFX were performed. Commercially available aortic valve replacements (AVR) 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 5.

Table 5 - 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.
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.

9.4 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.

9.5 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.

9.6 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 Ascendra Balloon Catheter and showed acceptable results: dimensional verification, visual inspection, simulated use, balloon characterization, bond strength, hemostasis, deployed valve diameter, and migration.

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

The following tests were performed for the Ascendra Introducer Sheath Set and showed acceptable results: dimensional verification, visual inspection, simulated use, bond strength, and hemostasis.

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

9.7 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 6.

Table 6 - 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 7.

Table 7 - 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 Performance	At 20 weeks, there were no differences from the average pre-explant peak gradients 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.

9.8 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.

9.9 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, Ascendra Balloon Catheter, Ascendra Balloon Aortic Valvuloplasty Catheter, Ascendra Introducer Sheath Set, and Crimper.

9.10 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, Ascendra Balloon Catheter, Ascendra Balloon Aortic Valvuloplasty Catheter, Ascendra Introducer Sheath Set, 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.

9.11 Product Integrity

9.11.1 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.

9.11.2 SAPIEN Valve Non-biological 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.

9.11.3 Delivery System and Accessories

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

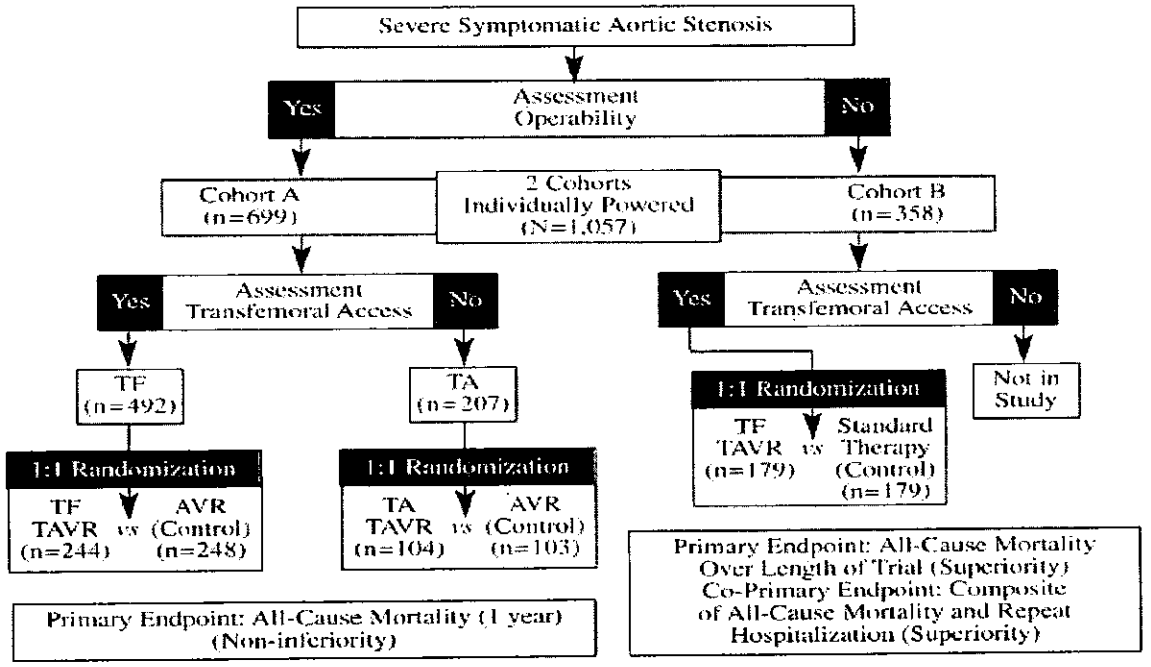
10. SUMMARY OF PRIMARY CLINICAL STUDY (G030069)

The applicant conducted 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 or transapical delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be at high risk 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.

10.1 Study Design

The PARTNER trial was a prospective, unblinded, randomized, controlled, multi-center pivotal trial evaluating the safety and effectiveness of the Edwards SAPIEN THV, via transfemoral (Cohort A and Cohort B) or transapical (Cohort A only) delivery. Because the study enrolled two distinct populations, the two Cohorts were separately-powered and analyzed. As depicted in the diagram below, an initial stratification based on operability for aortic valve replacement (AVR) surgery was used to assign the patients to Cohort A or B. Assignment to Cohorts was followed by determination of the possibility of vascular access for transfemoral delivery. Patients who were considered high surgical risk and eligible for transfemoral access were stratified into Cohort A and randomized to treatment (transfemoral AVR) or control (surgical AVR). Cohort A patients who were not eligible for transfemoral access were evaluated as candidates for transapical delivery and, if appropriate, randomized to treatment (transapical AVR) or control (surgical AVR). Those patients who were considered non-surgical candidates were stratified into Cohort B and randomized to treatment (transfemoral AVR) or control ("standard" 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. This PMA relates to only the Cohort A study.



AVR=aortic valve replacement surgery, TA=transapical. TAVR=transcatheter aortic valve replacement, TF=transfemoral.

Figure 8 - PARTNER Trial Enrollment

A total of 1057 subjects were enrolled at 27 sites in the PARTNER study in the two arms – 699 patients in Cohort A (transfemoral or transapical insertion of the SAPIEN compared to surgical AVR); 358 patients in Cohort B (transfemoral insertion of the SAPIEN versus "standard" therapy in an inoperable population).

The protocol was fully approved in March 2009 (Version 3.2), a few months before enrollment in Cohort A was complete (August 2009). In order to allow for continued access to a device when there may be a gap between trial completion and final regulatory review, additional patients who are still subject to the same patient protection measures as the IDE trial are enrolled under the "Continued Access Protocol (CAP)." These patients are enrolled into an "extension" of the initially approved sample size. The CAP was approved on August 13, 2009 for enrollment of Cohort A subjects in a non-randomized study.

The statistical analysis plan (SAP) included in Protocol Version 3.2 was finalized in March 2009. For this Cohort A study, FDA reviewed and assessed a dataset of events through September 21, 2011.

10.2 Patient Selection Process and Enrollment Criteria

The methodology for assessing patient risk incorporated the Society of Thoracic Surgeons (STS) risk calculator, and in addition, incorporated a minimum of two experienced surgeons and a cardiologist to make the initial high risk decision, taking into account risk factors not evaluated by the STS risk calculator. This decision was then peer reviewed on routine case review conference calls.

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

10.2.1 Inclusion Criteria

The major inclusion criteria for patient entry into the study included the following:

1) 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).
2) Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater.
3) Patients must have co-morbidities such that the surgeon and cardiologist Co-PIs concur that the predicted risk of operative mortality is ≥15% and/or a minimum STS score of 10. A candidate who does not meet the STS score criteria of ≥10 can be included in the study if a peer review by at least two surgeon investigators (not including the enrolling surgeon) concludes and documents that the patient's predicted risk of operative mortality is ≥15%. The surgeon's assessment of operative comorbidities not captured by the STS score must be documented in the study case report form as well as in the patient medical record.

10.2.2 Exclusion Criteria

The major exclusion criteria for patient entry into the study included the following:

1) Evidence of an acute myocardial infarction (MI) ≤ 1 month before the intended treatment (defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition).
2) Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
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).
4) Pre-existing prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification (MAC), severe (greater than 3+) mitral insufficiency, or Gorlin syndrome
5) Need for emergency surgery for any reason.
6) Native aortic annulus size < 18mm or > 25mm as measured by echocardiogram.
7) Patient has been offered surgery but has refused surgery.
8) Recent (within 6 months) cerebrovascular accident (CVA) or a transient ischemic attack (TIA).

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. This was an abbreviated listing of the main inclusion and exclusion criteria; there were a total of 29 entrance criteria for the subjects in this study.

10.2.3 Primary Safety and Effectiveness Endpoint

The primary effectiveness and safety endpoint for Cohort A was freedom from all cause mortality at exactly day 365, analyzed in the ITT population.

The hypotheses for the primary endpoint are:

$$H_0 : S_T(T) - S_C(T) \le -0.075$$
$$H_A : S_T(T) - S_C(T) > -0.075$$

where $S_T(T)$ is the freedom from all cause mortality at exactly day 365 for treatment arm and $S_C(T)$ is that for control arm.

The test statistic is $\frac{\hat{S}_{(T)}(T) - \hat{S}_{(C)}(T) + 0.075}{\sqrt{\hat{V}[\hat{S}_{(T)}(T)] + \hat{V}[\hat{S}_{(C)}(T)]}}$, where $\hat{S}_{(T)}(T)$ and $\hat{S}_{(C)}(T)$ are the survival rates estimated by the Kaplan-Meier algorithm, and $\hat{V}[\hat{S}_{(T)}(T)]$ and $\hat{V}[\hat{S}_{(C)}(T)]$ are the

variances estimated by Greenwood's formula. The null hypothesis will be rejected, and non-inferiority concluded, if the test statistic is greater than 1.645.

In addition to formal analysis of non-inferiority endpoints, the Kaplan-Meier (KM) curves will be presented for each group in the analysis, and a 95% two-sided confidence interval for the difference of the curves will be shown.

10.2.4 Secondary Safety and Effectiveness Endpoints

This section discusses pre-specified secondary safety and effectiveness endpoints as well as endpoints that are more clinically relevant. Both are described below.

10.2.4.1 FDA Secondary Endpoints

The following serious adverse event endpoints are considered to be clinically important, and should be interpreted in the context of the totality of data demonstrating safety and effectiveness of SAPIEN. Specifically the following adverse events were assessed at 1 year and will be presented in this summary:

- Deaths;
- Neurological Events;
- Aortic Regurgitation;
- Bleeding;
- Vascular Complications; and
- Atrial Fibrillation.

10.2.4.2 Pre-Specified Secondary Endpoints

The following, selected, pre-specified secondary endpoints are also interesting to note.

- 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)
  - Stroke
  - Renal failure
- Total hospital days from the index procedure to one year post procedure
- NYHA functional classification at 1 year
- Six minute walk test at 1 year

10.2.4.3 Other Secondary Endpoints of Interest:

1) Separate analyses of the primary endpoint in the transapical and transfemoral groups.
2) Functional improvement from baseline as measured per a) NYHA functional classification, b) effective orifice area (EOA) and c) six minute walk test at 30 days, six months and one year.
3) Freedom from MACCE at 30 days, 6 and 12 months. MACCE definition includes death, MI, stroke and renal failure.

4) Evidence of prosthetic valve dysfunction (hemolysis, infection, thrombosis, severe paravalvular leak or migration) at 30 days, 6 and 12 months.

5) Length of index hospital stay (ITT).

6) Total hospital days from the index procedure to one year post procedure (ITT).

7) Improved Quality of Life (QOL) from baseline at 30 days, 6 and 12 months (ITT).

8) Improved valve function demonstrated by a responder analysis showing the percentage of patients in each treatment group who have a greater than 50% improvement in AVA/EOA at 30 days, 6 and 12 months.

10.2.4.4 Other Adjunctive Analyses

In addition to the pre-specified primary endpoint at one year and several secondary endpoints evaluated at 30 days, 6 months, and/or 1 year, longer-term data are also presented. As part of the additional adjunctive analyses, 2 year data for mortality and major adverse cardiac and cerebrovascular events and findings related to the CAP cohort are included in this summary.

10.2.4.5 Comparison of Results to Sample Size Estimation

In calculating the sample size needed for the study, it was assumed that 65% of the patients would have the transfemoral approach (actual 70.4%). It was further estimated that the transfemoral patients would have improved 12-month mortality for the SAPIEN (25%) versus open AVR (30%). The study indicates a 12-month mortality of 22.24% for SAPIEN and 26.36% for open AVR on the transfemoral approach. It was assumed that for the transapical approach, the 12-month mortality would be 35% for both transapical TAVI and open AVR. The study indicates a 12-month mortality of 29.04% for transapical TAVI and 27.86% for open AVR.

10.3 Accountability of PMA Cohort

The study results are presented based on two populations: Intent-To-Treat (ITT) and As Treated (AT). There is also a third population, the Valve Implant population, consisting of those patients who received the valve. A summary of the patient populations is provided in the table below.

Table 8 - Summary of Cohort A Analysis Population (N=699 Total)

	Intent-to-Treat (ITT)	As Treated (AT)	Valve Implant
Treatment TAVI	n=348	n=344	n=326
Control AVR	n=351	n=313	n=311
Total	n=699	n=657	n=637

10.3.1 Intent-To-Treat Population

Of the 699 patients in the high risk, Cohort A, 348 were assigned to TAVI (SAPIEN) treatment group (244 of whom were implanted via the transfemoral route, and 104 of whom were implanted via the transapical approach), 351 were randomized into the AVR (control) group (248 of whom were eligible for transfemoral and 103 of whom were

eligible for transapical), forming the Intent To Treat (ITT) population, defined as all randomized patients.

10.3.2 As Treated Population

The As Treated (AT) population was based on the treatment actually received. Therefore, the As Treated population is defined as follows:

- *AT SAPIEN*: This population consists of the Cohort A patients randomized to the treatment arm for whom the study valve implant procedure is begun, and the day of implant is considered day 0 for these patients. The definition of "procedure is begun" is "the time the study catheter is placed in the patient in the catheterization laboratory."

  Four patients did not have an attempt at the procedure (i.e. ITT=348; AT=344)

  If a treatment patient in Cohort A was assigned to the transfemoral approach, and it was determined during further access evaluation that the transapical approach was needed, that patient was considered to be a transapical patient for the as treated analyses of implant subgroups. This did not impact the combined Cohort A analysis.

- *AT Control*: This population consists of the Cohort A patients randomized to the Control arm for whom the valve implant procedure was begun. The day of implant was considered day 0 for these patients. The definition of "procedure is begun" was "the induction of general anesthesia for the open operation." A total of n=38 patients were to have received a control valve, but did not (i.e., ITT = 351; AT = 313)

10.3.3 Valve Implant Population

The valve implant population is defined as the subset of the As Treated population consisting of those patients (Treatment or Control) for whom the valve was implanted and remained in position.

Among the AT patients, 18 TAVI patients did not have the valve in position at the end of 1 year. Thus, the valve implant population includes 326 patients in TAVI arm. Two AVR patients did not have the valve implanted.

This summary presents the data using the most appropriate treatment population for each particular analysis.

10.4 Study Population Demographics and Baseline Parameters

10.4.1 Baseline Demographics

The table below summarizes the baseline demographics for each group.

Table 9 - Patient Baseline Demographics

Characteristic	TAVI (SAPIEN) N=348	AVR (Control) N=351	*P*-value
Age (yr), mean±SD	83.6±6.8	84.5±6.4	0.07
Male sex, n (%)	201/348 (57.8)	198/351 (56.4)	0.82
STS score[b], mean±SD	11.8±3.3	11.7±3.5	0.61
NYHA (New York Heart Association) class, n/total n (%):			0.79
II	20/348 (5.7)	21/349 (6.0)	
III or IV	328/348 (94.3)	328/349 (94.0)	
Coronary artery disease, n/total n (%)	260/347 (74.9)	266/346 (76.2)	0.66
Previous myocardial infarction, n/total n (%)	92/347 (26.5)	103/346 (29.8)	0.35
Previous intervention, n/total n/total n (%)			
CABG (coronary artery bypass grafting)	148/348 (42.5)	152/349 (43.6)	0.82
PCI (percutaneous coronary intervention)	116/346 (33.5)	110/348 (31.6)	0.63
Balloon aortic valvuloplasty	46/348 (13.2)	35/349 (10.0)	0.20
Cerebral vascular disease, n/total n (%)	96/327 (29.4)	87/325 (26.8)	0.49
Peripheral vascular disease, n/total n (%)	149/345 (43.2)	142/341 (41.6)	0.70
COPD (chronic obstructive pulmonary disease), n (%):			
Any	152/348 (43.7)	151/351 (43.0)	0.88
Oxygen-dependent	38/220 (17.3)	38/229 (16.6)	0.90
Creatinine >2 mg/dl (177 µmol/liter), n/total n (%) [&]	37/343 (10.8)	22/344 (6.4)	0.04
Atrial fibrillation, n/total n (%)	81/199 (40.7)	75/172 (43.6)	0.60
Permanent pacemaker, n/total n (%)	69/348 (19.8)	76/349 (21.8)	0.58
Pulmonary hypertension, n/total n (%)	125/295 (42.7)	111/302 (36.8)	0.15
Extensively calcified aorta, n (%)	2/348 (0.60)	4/351 (1.1)	0.69
Deleterious effects of chest-wall irradiation, n (%)	3/348 (0.9)	3/351 (0.9)	1.00
Chest-wall deformity, n (%)	0/348 (0.0)	1/351 (0.3)	1.00
Frailty**	46/295 (15.6)	53/301 (17.6)	0.58
Liver Disease, n/total n (%)	8/348 (2.3)	11/349 (3.2)	0.64
Echocardiographic findings			
Aortic valve area – cm^2	0.7±0.2	0.6±0.2	0.11
Mean aortic valve gradient – mm Hg	42.6±14.6	43.5±14.3	0.42
Mean LVEF - %	52.5±13.5	53.3±12.8	0.59
Moderate or severe MR – n/total n (%)[#]	66/337 (19.6)	71/338 (21.0)	0.70

** Frailty was subjectively determined by surgeons using prespecified criteria for purposes of frailty score validation; see Section 10.8.14 for additional details

[&] To convert creatinine to micromoles/liter, multiply by 88.4.

[#] *Moderate to severe regurgitation was* defined as regurgitation of grade 3+ or higher

[b] The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.

Note that approximately 43% of the patients had a prior CABG, 10-13% had a prior balloon aortic valvuloplasty, 20% had a pacemaker, and 41-43% of patients had atrial fibrillation. The majority of the patients had been hospitalized for aortic stenosis in the past.

10.4.2 Operative Risk

The STS score predicted 11.7% for the 30-day mortality for the average surgeon at the average hospital. The Kaplan Meier (KM) 30-day mortality for the As Treated surgical AVR control was 8.0%. Therefore, the observed/expected ratio for the surgeons in this trial was 0.68 – indicating much better than average surgeons.

10.4.3 Patient Selection

10.4.3.1 Variations in patient selection

An enrollment screening log was kept at each investigative site. Overall, 27% of the patients screened in the trial were enrolled. The ratio of the number of patients screened to those excluded varied among the sites, as described in the table below.

Table 10 - Screening Results

Site	Ratio Screen failure/total screened	%
01	36/266	**14%**
18	58/146	40%
20	84/191	44%
09	251/403	62%
15	181/289	**63%**

10.4.3.2 Variations in site enrollment ratios of inoperable to high risk

There was a 3.4 fold variation in the enrollment ratio of transapical (TA) to transfemoral (TF), and a 4.3 fold variation in the ratio of "high risk" cohort A to "inoperable" Cohort B subjects between the sites, as depicted in the table below, which tabulates the ratios for the 6 highest enrolling sites.

Table 11 - Site Variability in Enrollment Ratios

Site Number	Cohort A Randomized TA Patients	Cohort A Randomized TF Patients	TA/TF Ratio	Cohort A Randomized PMA Patients	Cohort B Randomized PMA Patients	Cohort A/ Cohort B Ratio
01	40	55	0.73	95	21	4.52
02	25	72	0.35	97	33	2.94
04	22	25	0.88	47	45	1.04
08	29	38	0.76	67	43	1.56
09	23	29	0.79	52	21	2.48
10	24	92	0.26	116	36	3.22

10.5 Primary Safety and Effectiveness Endpoint Results

The following section focuses on an analysis of the primary safety and effectiveness endpoint which evaluates freedom from mortality at one year. There are also discussions of the gender analysis for the primary endpoint, and a review of the differences in mortality between the transfemoral and transapical groups.

10.5.1 Results of Primary Endpoint - Freedom from All Cause Mortality at One Year

At the end of 1 year, there were 84 (out of 348) and 89 (out of 351) deaths in the TAVI and AVR arm in the ITT population, respectively. The Kaplan-Meier estimates of the all-cause mortality rate at 1 year are stated to be 24.27% and 26.80% for the TAVI

(treatment) and AVR (control) arm, respectively. The survival difference (TAVI-AVR) was 0.0253, and the 95% one-sided lower confidence limit (CL) for the difference was -0.0299, which is greater than the pre-defined non-inferiority margin (-0.075). The p-value for the non-inferiority test is 0.0014, indicating that the primary endpoint is met with a 0.075 non-inferiority margin.

In addition to the 1 year data, patient outcomes at 2 years are also presented, allowing for an assessment of longer-term results of SAPIEN THV implantation. The Kaplan-Meier cumulative incidence curve for the all-cause mortality to two years is shown below for the ITT population. The Kaplan-Meier estimates of the all-cause mortality rate at 2 years are stated to be 41.3% and 35.5% for the TAVI (treatment) and AVR (control) arm, respectively.

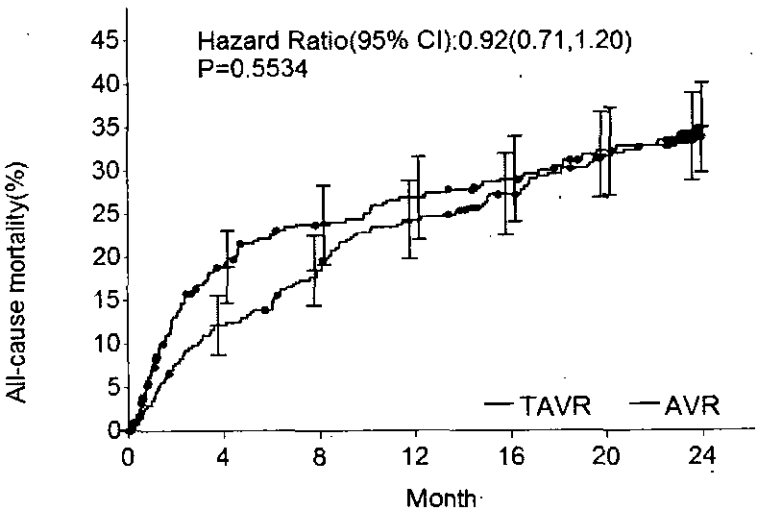


Figure 9 - Kaplan-Meier Cumulative Incidence Curve for All-Cause Mortality (ITT Population)

Based upon these data, there is no significant difference in mortality between the treatment and control groups at the 1 year endpoint. A careful review of the death narratives for this study did not raise any specific concerns regarding the causes of death in this study.

10.5.2 Analysis of AT Population

For the AT population, at the end of 1 year, there were 81 (out of 344) and 78 (out of 313) deaths in the TAVI and AVR arm, respectively. The Kaplan-Meier estimates of the all cause mortality rate at 1 year are stated to be 23.7% and 25.2% for the TAVI (treatment) and AVR (control) arm, respectively. The survival difference (TAVI-AVR) was -1.5, and the 95% one-sided lower CL for the difference was -0.004, which is greater than the pre-defined non-inferiority margin of -7.5%. The p-value for the non-inferiority test is 0.0037, indicating that the primary endpoint is met with a 7.5% non-inferiority margin on the AT population.

10.5.3 Site Poolability for the Primary Endpoint

Center effect on the primary endpoint was evaluated by the sponsor using Cox regression. Using Site 01 as the reference group, hazard ratios of different sites over the reference group were reported for ITT population and for AT population. Except for one center (Site 15), all other 95% CI of center hazard ratios include 1. Site 15 contributes 25/699 = 3.58% of the ITT subjects in the database and 20/657=3.0% of the AT subjects.

A logistic regression model containing treatment, site, and treatment by site interaction is performed on all-cause mortality as well as on MACCE. No significant interaction is detected on either endpoint (p-value > 0.15).

10.5.4 Gender Differences for Primary Endpoint

A *post hoc* analysis was conducted to compare mortality between genders. The study was not powered for each gender separately.

In the ITT population, males composed 57.8% (201/348) of TAVI arm and 56.7% (198/351) of AVR. In the AT population, males were 57.6% (198/344) of TAVI arm and 57.2% (179/313) of AVR.

In both ITT and AT populations, males performed better with AVR. All-cause mortality was numerically higher in the TAVI arm than that in the AVR arm. The mortality rates at 1 year are 28.52% and 25.21% for TAVI and AVR, respectively, in the ITT population. The mortality rates at 1 year are 27.44% and 22.67% for TAVI and AVR, respectively, in the AT population. The 95% one-sided lower confidence limits of survival difference (TAVI-AVR) are -10.69% and -12.14% for ITT and AT, respectively. Both are less than the pre-specified non-inferiority margin (-7.5%).

In both ITT and AT populations, females perform better with TAVI. All-cause mortality was numerically higher in the AVR arm than that in the TAVI arm. The mortality rates at 1 year are 18.45% and 29.03% for TAVI and AVR, respectively, in the ITT population. The mortality rates at 1 year are 18.58% and 28.56% for TAVI and AVR, respectively, in the AT population. The 95% one-sided lower confidence limits of survival difference (TAVI-AVR) are 2.36% and 1.64% for ITT and AT, respectively. Both are greater than the pre-specified non-inferiority margin (-7.5%).

Table 12 - One-Year All-Cause Mortality in Males Vs. Females

Group	Intent to Treat			As Treated		
	TAVI	AVR	95% LCL*	TAVI	AVR	95% LCL*
Male	28.52%	25.21%	-10.69%	27.44%	22.67%	-12.14%
Female	18.45%	29.03%	2.36%	18.58%	28.56%	1.64%

* Pre-specified non-inferiority margin -7.5%

In the continued access protocol (CAP) cohort, 1588 patients were enrolled in the TAVI registry (since randomization was eliminated for the CAP cohort) and 770 of them are female (48.5%). At one year, the K-M estimated event rates in ITT population are

18.54% for females and 25.94% for males, respectively. Those numbers are numerically close to those observed in the randomized study (18.45% and 28.52%, respectively).

Although this study was not powered for each gender separately, it appears that treatment effects are in the opposite direction for males versus females.

10.5.5 Transfemoral and Transapical Approaches

Though the interaction of treatment and approach (transfemoral versus transapical) is tested and is found to be not significant (p-value > 0.15), separate analyses of the primary endpoint in the transapical and transfemoral groups are of interest and are presented here for both the ITT and AT groups.

10.5.5.1 Transfemoral Approach

In the ITT population, for the transfemoral approach, there were 244 patients and 248 patients in the treatment and control groups, respectively. For the all cause mortality, the KM event rates at 1 year are 22.24% and 26.36% for the transfemoral treatment group and control group, respectively. The survival difference is 4.12% (Transfemoral-Control). The 95% one-sided lower CL for the survival difference is -2.34%.

In the AT population, for the transfemoral approach, there are 240 patients and 221 patients in the treatment and control groups, respectively. For the all cause mortality, the KM event rates at 1 year are 21.35% and 25.18% for the transfemoral treatment group and control group, respectively. The survival difference is 3.83% (Transfemoral-Control). The 95% one-sided lower CL for the difference is -2.68%.

10.5.5.2 Transapical Approach

In the ITT population, for the transapical approach, there were 104 patients and 103 patients in the treatment and control group, respectively. For the all cause mortality, the KM event rates at 1 year are 29.04% and 27.86% for the transapical treatment group and control group, respectively. The survival difference is -1.18% (Transapical-Control). The 95% one-sided lower CL for the difference is –11.69%.

In the AT population, for the transapical approach, there are 104 patients and 92 patients in the treatment and control group, respectively. For the all cause mortality, the KM event rates at 1 year are 29.07% and 25.28% for the transapical treatment group and control group, respectively. The survival difference is -3.79% (Transapical-Control). The 95% one-sided lower CL for the difference is -14.29%.

The mortality rates are numerically higher in the treatment group for the transapical approach.

There were limited patients in the transapical arm of the IDE randomized clinical trial (RCT). The final assessment of transapical delivery is presented later where the totality of the IDE RCT and CAP data are assessed.

Table 13 - One-Year All-Cause Mortality in Transfemoral Vs. Transapical

Group	Intent to Treat			As Treated		
	TAVI	AVR	95% LCL	TAVI	AVR	95% LCL
Transfemoral	22.24%	26.36%	-2.34%	21.35%	25.18%	-2.68%
Transapical	29.04%	27.86%	-11.69%	29.07%	25.28%	-14.29%

10.6 Limitations of Interpretation of Study Results

The interpretation of the results of this study is not without limitations. The following sections discuss special considerations to note when interpreting the data. The impact of these limitations on overall data interpretation is unknown.

Sensitivity Analyses for ITT Population

The Sponsor performed a worst case analysis to assess the robustness of the mortality results. The assumption used in the worst case analysis was that AVR patients who were censored prior to 1 year were considered alive at 1 year, and AVR patients who did not receive the procedure were also considered alive at 1 year; and that TAVI patients who were censored prior to 1 year were considered dead as of the censoring date, and TAVI patients who did not receive the procedure were also considered dead at 1 year.

The primary endpoint of all-cause mortality is still met with a 0.075 non-inferiority margin on the worst case analysis.

Although the primary endpoint was met, issues related to potential selection bias and other study limitations described below should be considered when interpreting these results.

Patient Treatment

The following section highlights FDA's interpretation of data related to patient treatment.

10.6.1 Heterogeneity of Treatment

This trial was designed to compare isolated AVR to TAVI. However, a review of the data resulted in a comparison that includes a heterogeneous group of patients and a combination of therapies as shown in the figure below.

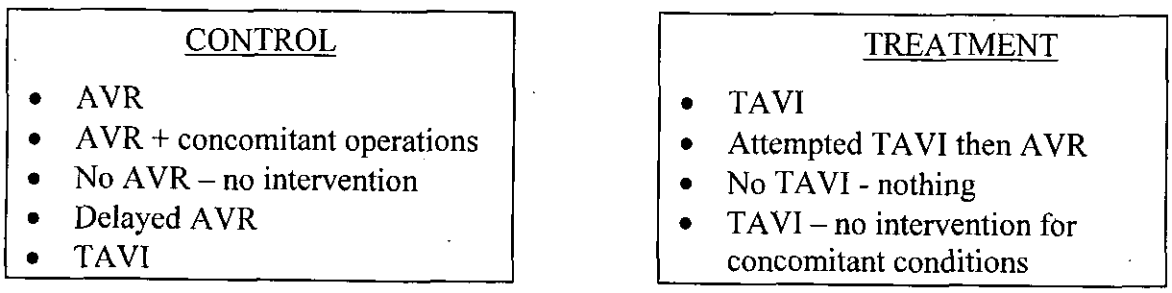


Figure 10 - Heterogeneity of Treatment

Due to the heterogeneity of treatment control group, interpretability of any differences between patient groups is limited. The following sections more fully described the following:

1. Failure to attempt to treat;
2. Delay in treatment; and
3. 3.Concomitant operations.

Results are confounded by the issue of AVR patients not receiving AVR, TAVI patients receiving AVR, and AVR patients undergoing concomitant operations.

10.6.2 Failure to Attempt to Treat

10.6.2.1 Imbalance in Failure to Attempt to Treat

There was an imbalance between the control and treatment groups as to those patients who refused/withdrew (28 fold increase in AVR group), patients who died before the procedure (2.3 fold increase in AVR group), and those judged to have deteriorated (5 fold increase in AVR group). The table below demonstrates the issue of differential numbers of failure to treat.

Table 14 – Reasons for Failure to Treat

Reason	TAVI (N=348)	AVR (N=351)
Died before the procedure	2 (0.6%)	5 (1.4%)
Refusal	1 (0.3%)	17 (4.8%)
Withdrawal	0 (0%)	11 (3.1%)
Pre-treatment deterioration	1 (0.3%)	5 (1.4%)
Total	4 (1.1%)	38 (10.8%)

Only 3/28 of the patients who refused AVR or withdrew from the study were known to be dead at one year (one patient refused AVR because she "started feeling better").

It cannot be assumed that the sickness of the patients who chose to withdraw from the study was the same as those who were treated. If less sick patients differentially withdrew from the AVR arm, this could possibly bias results towards the treatment group in an Intent-to-Treat analysis. The imbalance between reasons for failing to treat patients has the potential of introducing selection bias in both the ITT and As Treated (AT) analyses.

This phenomenon of failure to treat in the control group occurred differently at various sites, as is shown in the table below.

Table 15 - Percentage of Randomized Control Patients Not Receiving AVR (Sites enrolling >25 control patients)

Site	**10**	**02**	**08**	**04**	**15**
Total control pts enrolled at site	116	97	67	47	25
# control pts not getting AVR	1	5	6	5	5
% pts not getting control AVR	1%	5.1%	9.0%	10.6%	20%

Almost 11% of the patients did not get the assigned treatment in the AVR group.

Because these patients had critical aortic stenosis, it was expected that they would be treated per the group to which they were assigned and be indicated for isolated valve replacement. The trial results are confounded as a result of failing to treat these patients, possibly indicating a biased result towards worse outcomes in the ITT AVR group, because some patients did not receive the recommended treatment for their disease and the issue of concomitant operations in the AVR group. This could also bias results of the As Treated analysis against the AVR group if those patients not treated were "less sick" and therefore were excluded from the As Treated analysis, or if those patients had concomitant operations. These data need to be interpreted carefully since patient treatment across sites was not homogenous due to the large variation in the rates of Failure to Treat among sites.

10.6.2.2 Imbalance in Failed Treatment

In the TAVI group, a total of n=18 SAPIEN patients were excluded because either the SAPIEN was never implanted or did not remain *in situ* at the end of the index procedure, as detailed in the following table.

Table 16 – Reasons for Unsuccessful TAVI

Reasons for Unsuccessful TAVI	Status	n
Valve embolization	Did not remain *in situ*	5
TEE findings	Not implanted	5
Access problems	Not implanted	4
Died prior to valve deployment	Not implanted	2
Femoral artery tear	Not implanted	1
Large sigmoid septum	Not implanted	1
Total		18

In the control AVR group two patients were operated on but did not receive a valve. One patient had a severely calcified aorta and subsequently underwent TAVI (alive at one year) and another needed a reoperation and died during the procedure.

There is an imbalance in patients who had attempted treatment that did not result in an implanted valve. Similar to earlier comments, the impact of these events on overall data interpretability is unknown.

10.6.2.3 Cross-Over - Use of AVR in TAVI arm

There were a total of 11 AVR procedures performed in patients randomized to TAVI, several of which were emergency procedures. These patients are summarized below:

i. Not implanted because of congenital septal condition
ii. Annulus 26mm, converted to AVR
iii. Annulus >25mm, converted to AVR done
iv. SAPIEN embolized to LV, emergency AVR (multiple complications)

v. SAPIEN embolized to LV, emergency AVR (multiple complications)
vi. SAPIEN embolized to LV, emergency AVR (multiple complications)
vii. Annulus 27mm, converted to AVR done
viii. SAPIEN embolized to LV, emergency AVR (patient died)
ix. SAPIEN embolized to descending aorta, emergency AVR (multiple complications)
x. Aortic dissection during attempted TAVI, AVR 3 mos later abandoned due to access procedures, AVR 3 mos later

These patients were included in TAVI arm for both the ITT and AT analyses. The impact of these patients on the overall results is unknown since the beneficial effects of AVR could possibly introduce bias in favor of the TAVI arm. FDA also notes that in the TAVI arm, these patients would have remained untreated for their critical aortic stenosis without the use of open AVR as a bailout procedure. It should also be noted that converting a patient from an elective TAVI to an emergency AVR is known to increase the risk of mortality.

10.6.2.4 Delay in Treatment

In the TAVI group, there was a mean 11-day delay from randomization to the procedure, whereas in the AVR group the mean delay was 16 days. The data also show that more patients in the control group had a considerable delay between randomization and treatment than in the treatment group. For instance, one patient did not have AVR because of "worsening lab values" – however, this occurred 14 months after randomization.

The impact of delay in treatment on results is difficult to interpret, but could have confounding effects on the assessment of overall safety and effectiveness.

10.6.2.5 Concomitant Operations in the AVR group

This trial was intended to compare isolated open AVR to isolated TAVI. The inclusion/exclusion criteria specifically excluded patients from the study with "Untreated coronary artery disease (CAD) requiring revascularization." However, 21 patients (6.7%) in the AVR group had a concomitant coronary artery bypass (CAB) procedure. Patients with CAD remained untreated in the SAPIEN group.

In addition, multiple exclusion criteria were intended to exclude the need for operation for associated conditions. However, concomitant operations for associated conditions were performed in 12.8% (40/313 AT) of the control patients. These data are provided in the table below.

Table 17 - Concomitant Operations

CABG	20
CABG + aortic endarterectomy	1
MV repair	4
MV replacement	1
MV repair, annular enlargement	1
MV repair, root enlargement	1
TV repair	1
TV annuloplasty, Root replacement	1
Root/arch replacement	3
Aortoplasty	2
Ascending Aortic endarterectomy	3
Ablation for afib	1
Excision Left Atrial Appendage	1
TOTAL Patients with concomitant operations (% total 40/313) (As Treated)	40 (12.8%)

Of the 40 patients who underwent concomitant operations in the control group, 42.5% (17/40) had died by 1 year.

The operative risk of combination operations (AVR+CAB, AVR+ other valves, ablation, etc.) is known to be higher than for isolated valve procedures. This higher operative risk could bias safety results in a short-term study. Patients randomized to the SAPIEN group who were untreated for these concomitant conditions could affect long-term results for TAVI, but might not be captured in this shorter term study. This could introduce bias in favor of the treatment group in both the ITT and AT analyses because of the short-term increased risk of concomitant operations and because the long-term effectiveness of treating these conditions were not captured by the short-term (1 year) primary effectiveness endpoint.

10.6.2.6 Lack of Standardized Antithrombotic Treatment in the AVR population

There were no pre-specified antithrombotic regimens in the control group in the protocol for this study. The following regimen for antithrombotic drugs was provided for the TAVI arm.

Table 18 - Recommended Medication Regimen

Medication	Pre-Procedure	During Catheterization	Post-Procedure	30-Day Follow-up	6 month follow-up
IV Heparin	PRN	5000 IU bolus, then as needed to achieve/maintain ACT ≥250 sec			
Aspirin	75-100 mg QD		75-100 mg QD	75-100 mg QD	75-100 mg QD
Clopidogrel*	300 mg (if not on long-term therapy)	75 mg QD	75 mg QD	75 mg QD for 6 months	

* Ticlopidine could be used instead of clopidogrel at the investigator's discretion

The non-protocolized antithrombotic regimen resulted in important variations between the two arms of the trial, especially in the use of clopidogrel in the larger transfemoral arm. The following table presents the actual antithrombotic use over the first year.

Table 19 - Actual Medication Regimen

Medication	Randomized Patients (% pts)				
		Transapical		Transfemoral	
	Visit	AVR (N=103)	SAPIEN (N=104)	AVR (N=248)	SAPIEN (N=244)
Aspirin	Baseline	64/103 (62.1%)	64/104 (61.5%)	150/248 (60.5%)	166/244 (68.0%)
	1 yr	52/103 (50.5%)	62/104 (59.6%)	143/248 (57.7%)	171/244 (70.1%)
Clopidogrel	Baseline	29/103 (28.2%)	25/104 (24.0%)	42/248 (17.0%)	52/244 (21.3%)
	1 yr	19/103 (18.4%)	22/104 (21.2%)	26/248 (10.5%)	72/244 (29.5%)
Warfarin	Baseline	21/103 (20.4%)	19/104 (18.3%)	50/248 (20.2%)	49/244 (20.1%)
	1 yr	8/103 (7.8%)	11/104 (10.6%)	17/248 (6.9%)	28/244 (11.5%)

The lack of a standardized antithrombotic protocol in the AVR arm makes evaluation of the post-procedural stroke rate difficult to interpret. There are currently no approved antithrombotics labeled for TAVI.

10.6.2.7 Missing Data

For several of the parameters, notably 6-minute walk and NYHA, there was a significant amount of missing data collected for the parameter.

10.7 FDA Clinically Important Endpoints

10.7.1 Serious Adverse Events

The following table summarizes the Serious Adverse Events (SAEs) that occurred in this study during the 30 day post-operative period, 31 days to 1 year, overall events from 0 days to 1 year, and events occurring beyond 1 year:

Table 20 - Serious Adverse Events (AT Population)

Outcome	30 Days		31 Days – 1 Year		0 Days – 1 Year		> 1 Year	
	Pooled TAVI (N=344)	Pooled AVR (N=313)	Pooled TAVI (N=325)	Pooled AVR (N=284)	Pooled TAVI (N=344)	Pooled AVR (N=313)	Pooled TAVI (N=259)	Pooled AVR (N=229)
Death	18(5.2%)	25(8.0%	63(19.4%)	53(18.7%	81(23.5%)	78(24.9%)	49(18.9%)	42(18.3%)
All Stroke	15(4.4%)	8(2.6%)	4(1.2%)	1(0.4%)	19(5.5%)	9(2.9%)	4(1.5%)	8(3.5%)
Myocardial Infarction	0(0.0%)	1(0.3%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)	2(0.8%)	5(2.2%)
Major Vascular Complication	38(11.0%)	12(3.8%)	0(0.0%)	0(0.0%)	38(11.0%)	12(3.8%)	1(0.4%)	0(0.0%)
Renal Failure	13(3.8%)	14(4.5%)	4(1.2%)	5(1.8%)	17(4.9%)	19(6.1%)	2(0.8%)	0(0.0%)
Major Bleeding (CEC)	37(10.8%)	72(23.0%)	20(6.2%)	14(4.9%)	52(15.1%)	84(26.8%)	11(4.2%)	12(5.2%)
New Atrial Fibrillation	30/321 (9.3%)	57/290 (19.7%)	14/254 (5.5%)	3/190 (1.6%)	44/326 (13.5%)	60/294 (20.4%)	N/A	N/A
New Pacemaker	16(4.7%	14(4.5%)	4(1.2)	2(0.7%)	20(5.8%)	16(5.1%)	2(0.8%)	3(1.3%)
Presence of Mild or greater (>1+) aortic insufficiency	229/334 (68.6%)	53/287 (18.5%)	174/268 (64.9%)	36/197 (18.3%)	250/336 (74.4%)	64/293 (21.8%)	47/97 (48.5%)	9/77 (11.7%)

A more detailed review of some of these events is discussed in the next sections.

10.7.2 Deaths

Table 21 - Death Event Rates by Implant Approach in Treatment and Control Group (ITT Population)

Implant Approach	Study Arm	Number of Patients Who Died at 12 months
Transfemoral	TAVI (N=244)	54
	Open AVR (N=248)	62
Transapical	TAVI (N=104)	30
	Open AVR (N=103)	27
Pooled	TAVI (N=348)	84
	Open AVR (N=351)	89

Evaluation of these results must take into consideration the trial conduct issues such as the 10% of patients not getting AVR, the inclusion of the 11 patients in the TAVI arm who received AVR, and the confounding issue of concomitant operations in 13% of the AVR arm.

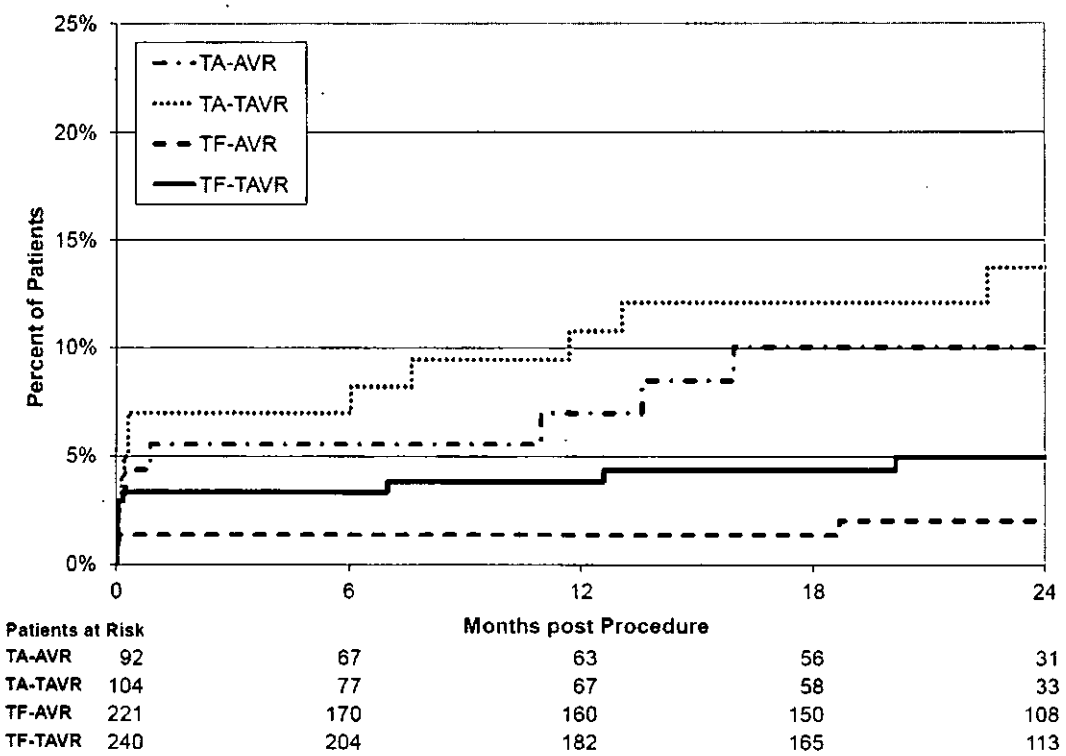
There was an increase in mortality in patients undergoing transapical delivery of SAPIEN THV.

10.7.3 Neurological Events

The agreed upon, pre-specified definition of stroke was as follows:

A stroke is a neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction.

Figure 11 shows the percentage of patients who had a stroke at various timepoints. This figure includes patients who were in the control group and received AVR and those patients in the treatment group receiving the SAPIEN THV via the transfemoral and transapical approaches.



Patients at Risk					
TA-AVR	92	67	63	56	31
TA-TAVR	104	77	67	58	33
TF-AVR	221	170	160	150	108
TF-TAVR	240	204	182	165	113

Figure 11 - Stroke Incidence in As Treated Cohort A Patients

Comparing open AVR and SAPIEN TAVI, there is a doubling of the neurological event rate in the SAPIEN patients in the acute periprocedural period (0-30 days). The transapical patients had higher neurological events rates than transfemoral delivery in both groups. For the transfemoral arm, it appears that the TAVI and AVR curves are parallel after the acute period, thus indicating no difference in stroke rates chronically. However, with the transapical approach, there appears to be both an increased early stroke rate and an increased stroke rate chronically. Neurological adverse events remain an important safety consideration for this device, and should be weighed in the overall determination of safety and effectiveness for the SAPIEN device.

The cause of neurological injury with transcatheter valve implantation is multifactorial. One important consideration is management of antithrombotics. The PARTNER trial did not require patients to be on a protocolized antithrombotic regimen. While this may aid in reducing the neurological event risk for patients receiving the SAPIEN, other risk mitigation measures may also need to be taken into account.

10.7.4 Aortic Regurgitation (AR)

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

Table 22 - Mild, Moderate or Severe Total Aortic Regurgitation (% Patients)

Pooled	30day	6 month	1 yr
AVR	16.5	14.3	13.9
SAPIEN	62.2	60.2	55.8

Table 23 - Moderate or Severe Aortic Regurgitation (% Patients)

Pooled	DC	30day	6 month	1 yr	2 yr
AVR	1.2	1.7	1.1	2.5	1.3
SAPIEN	10.2	14.8	14.8	9.3	8.2

The following figure shows the correlation between aortic insufficiency and death in the present study.

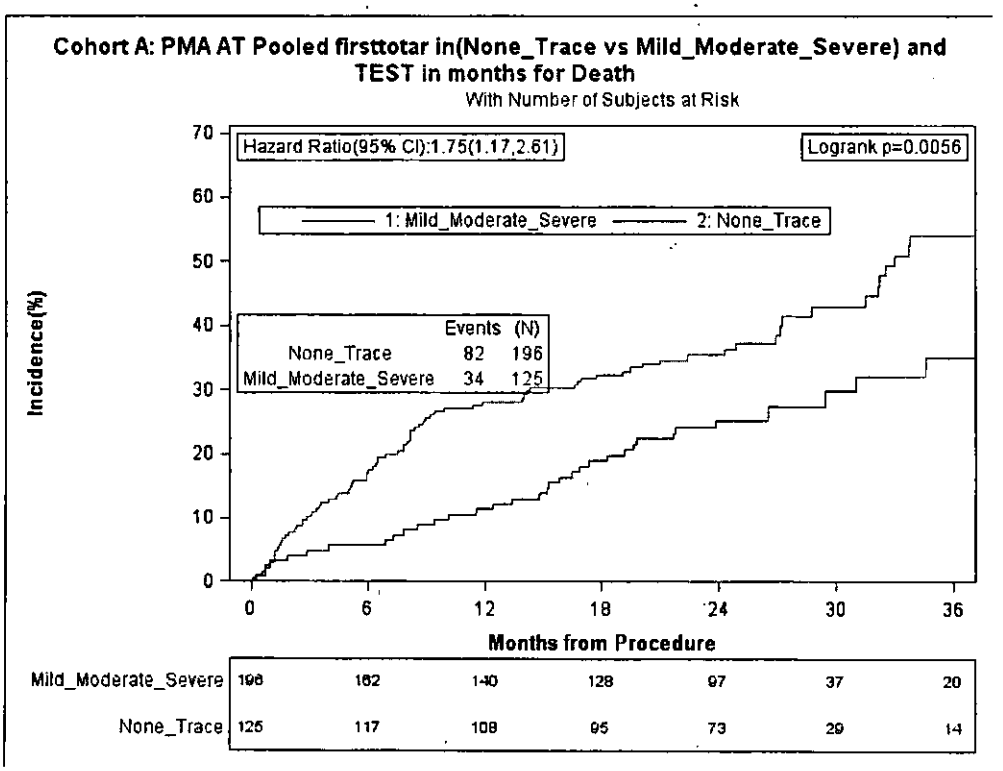


Figure 12 -Mortality Risk of Mild/Moderate/Severe Perivalvular Leak in TAVI Patients

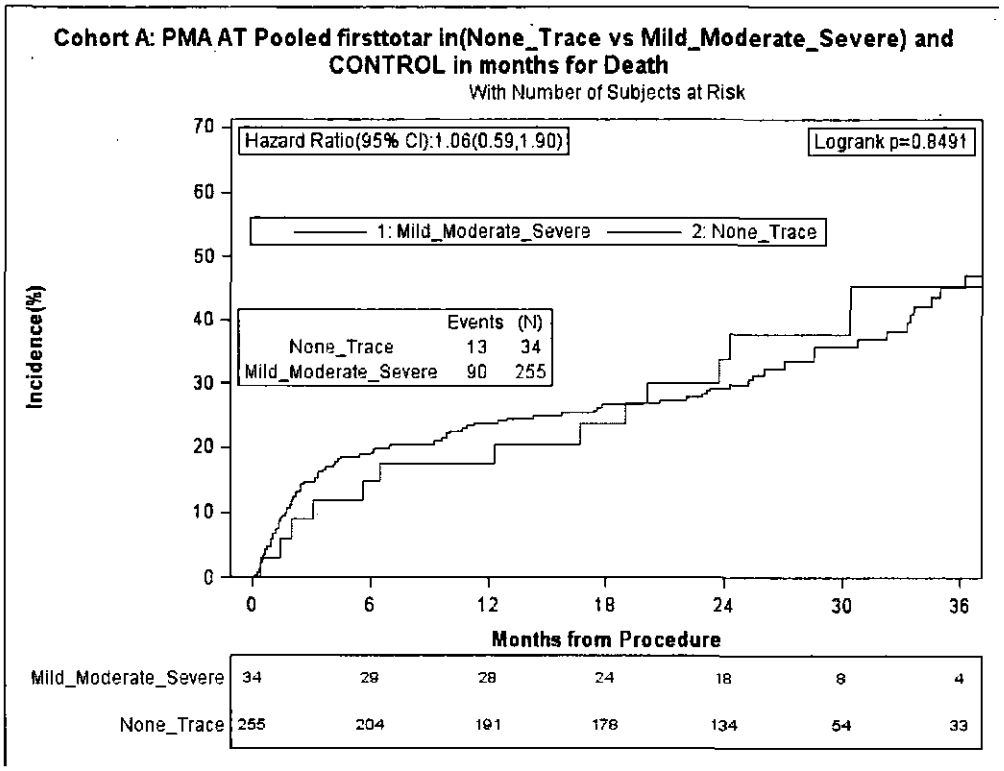


Figure 13 - Mortality Risk of Mild/Moderate/Severe Perivalvular Leak in Control AVR Patients

This study was not powered to detect differences between AVR and TAVI with regard to AR; however, there may be a relationship between these factors. Regardless, chronic aortic regurgitation occurs in a sizeable minority of TAVR patients. Based on the data from this trial and other recent literature[1-3] aortic regurgitation in the TAVI patient population appears to impact long-term survival. The chronic incidence of aortic regurgitation and its apparent impact on late term survival will be carefully monitored in the post-approval study. It will also be important to determine if improved acute procedural techniques impact this relationship.

10.7.5 Bleeding

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

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 PRBCs or pericardiocentesis procedure. The complication *bleeding event* applies to all patients whether or not they are taking antithrombotic drugs, since bleeding events can occur in patients who are not receiving antithrombotics. 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. Events which are excluded are: those due to liver disease, myocardial infarction, or systemic infection.

Since blood transfusions are a marker for mortality[4], they are important to track. In this study with a primary endpoint of mortality at one year, the major effect of blood

transfusion on mortality is captured within the primary endpoint. However, there is a dramatic 3.5 fold variability in blood transfusion between sites (as shown in Table 24) and indicates that blood conservation techniques at many of the sites may not have been optimal and/or consistent. This represents an area for improvement in the surgical treatment of aortic valve disease.

Table 24 - Site Variability in Major Bleeding in Control AVR (Sites with >20 control cases)

Site #	%controls with Major Bleeding
08	43
01	32
03	30
02	21
10	13
09	12

10.7.6 Vascular Complications

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

Aortic Dissection:

Aortic dissection defined as Type A or B dissections that require surgical or percutaneous 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

From the table below, vascular injury was present in 5.4% (17/313) of AVR patients and 17.7% (61/344) of the SAPIEN TAVI patients in the AT analysis.

Table 25 – Vascular Complications in the AT Population

Vascular Complication	TA-AVR	TA-TAVI	TF-AVR	TF-TAVI
Hematoma at access site >5cm	1	0	2	12
False aneurysm	0	1	2	4
Arterio-venous fistula	0	0	0	2
Retroperitoneal bleeding	0	0	1	4
Peripheral ischemia/nerve injury	0	0	0	0
Vascular Surgical Repair	6	4	5	34
Total	7	5	10	56

It appears that 19% 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 26 - Vascular Complication Types in the AT Population

Vascular Complication in SAPIEN (CEC adjudicated)	**#events**
Myocardial perforation	3
VSD	1
Thoracic aortic dissection	3
Abdominal aortic dissection	1
Iliac or Ileofemoral artery dissection	16
Femoral artery dissection	11
Iliac artery perforation	6
Femoral artery perforation	6
Femoral pseudoaneurysm	6
Iliac or femoral artery embolus	7
Femoral or retroperitoneal hematoma	16
AV fistula	2
Total Events	**78**
# patients with Vascular Complication	**64**
Total patients	**344**
% patients with vascular complication	**18.6%**

The study results indicated that 19% of the SAPIEN TAVI patients had serious adverse events relating to the access procedure. These injuries most often resulted in the need for prosthetic material and/or graft repair of the injuries. These patients remain at risk of graft thrombosis and infection throughout the remainder of their lives, a long-term risk that should be closely monitored in the post-approval setting.

10.7.7 Atrial Fibrillation (AF)

For AF, data on new onset of AF were provided but this was not analyzed according to the presence of AF at each time period. Short (e.g. minutes) events of AF were counted the same as the permanent or persistent atrial fibrillation for the sponsor's "new onset AF" endpoint.

The following table provides the occurrence of AF at the 6 month and one year follow-up visit.

Table 27 - Patients with No AF at Baseline Who Developed AF at Scheduled Follow-Up Exam (AT Population, n = not censored as of 6 months or 1 year visit)

	AVR %	SAPIEN %	Relative Risk SAPIEN/AVR	Missing Data AVR %	Missing Data SAPIEN %
6 month visit (Control n=162, SAPIEN n=208)	7/162 (4.3%)	12/208 (5.8%)	1.35	51/162 (31.5%)	45/208 (21.6%)
1 year visit (Control n=155, SAPIEN n=185)	4/155 (2.6%)	14/185 (7.6%)	2.92	59/155 (38.1%)	41/233 (17.6%)

Table 28 - Patients with AF at Baseline Who Did Not Have AF at Scheduled Follow-Up Exam (AT Population, n = not censored as of 6 months or 1 year visit)

	AVR %	SAPIEN %	Relative Risk SAPIEN/AVR	Missing Data AVR %	Missing Data SAPIEN %
6 month visit (Control n=54, SAPIEN n=65)	19/54 (35.1%)	12/65 (18.5%)	0.53	19/54 (35.2%)	11/65 (16.9%)
1 year visit (Control n=49, SAPIEN n=55)	15/49 (30.6%)	13/55 (23.6%)	0.77	16/49 (32.6%)	5/55 (9.1%)

There is a higher incidence of transient AF (new onset" atrial fibrillation in the open AVR group defined as short events, e.g. >30 seconds), but these data do not indicate how many patients are in atrial fibrillation at each follow-up visit. Other than hospital stay, there are no proven chronic consequences of transient postoperative atrial fibrillation.

When AF is captured at the chronic visits, it was numerically more likely that control patients who had AF at entrance into the study would be out of AF after open AVR than those patients in the SAPIEN TAVI group. Also, it was numerically more likely that patients without AF at baseline treated with the SAPIEN would develop AF at the chronic follow-up examinations.

10.8 Other Endpoints

10.8.1 Endocarditis

There were 5 cases of endocarditis in the AVR and 5 cases in the TAVI patients.

10.8.2 Device Malfunctions

Device malfunction was experienced in 5 patients. Four of five malfunctions were due to the delivery system. The fifth event was a case where two of the leaflets were not functioning after implantation, and this patient died.

FDA has no concerns regarding the data provided for device malfunction. FDA continues to emphasize the need for appropriate training and labeling to mitigate risks associated with device malfunction.

10.8.3 Other Serious Adverse Events

Data were also collected for the following important adverse events: myocardial infarction, renal failure (chronic dialysis for >30 days), renal insufficiency (creatinine >3.5), bradyarrhythmic event, and mitral valve compromise. There is no difference between arms in these complications.

10.8.4 Device Success/Procedure Success

Device success is evaluated on Valve Implant Population. Device success was defined as successful delivery and deployment of the device and retrieval of the delivery catheter resulting in an aortic valve area greater than $0.9cm^2$ with < 3+ aortic regurgitation in the earliest evaluable echocardiogram (which may not be the same echocardiogram for both parameters) and only one valve is implanted in the correct anatomical position. In the TAVI group, 17.2% (56/326) of the valve implant population did not have device success and 1.23% (4/326) could not be evaluated. This does not count the 18 patients who had the procedure attempted but in whom the valve did not remain *in situ*. The following are the reasons:

Table 29 - Device failure

Reason for No Device Success	# of Patients
Aortic Regurgitation >2+	34
Aortic Valve Area $\leq 0.9cm^2$	13
More than 1 TAVI used	7
Two or more of above	2
Not implanted or not *in situ* at end of procedure	18

Procedure success is evaluated on Valve Implant Population. Procedure success was defined as Device Success + no 30-day MACCE. Out of 326 patients, 25% (n=82) of the patients did not have Procedure Success. The reasons for lack of procedure success were no Device Success in 55 patients and MACCE in 27 patients.

These data show that 100 out of 344 (29%) TAVI patients who had the procedure attempted (AT population) either failed to have the valve implanted, failed to have Device Success, or failed to have Procedure Success.

The table above is based on the sponsor's definition of AR >2+. However, the FDA prospectively defined a lack of success as AR > 1+. FDA requested this information, but it was not provided for review.

10.8.5 Quality of Life

At 30 days, there was a statistically significant difference, in favor of TAVI. At 1 year, there is no clinically important difference in any of the sub-components of the KCCQ.

FDA cautions interpretation of these results in the setting of an unblinded trial, particularly in a comparison of patients undergoing open heart surgery versus patients receiving TAVI.

10.8.6 Follow-Up Time

The mean follow-up time for the primary endpoint is 1.6 ±1.0 years for the pooled AVR and 1.8±1.0 years for TAVI. The Sponsor has provided additional data out to 2 years for certain endpoints.

FDA believes that this is insufficient follow-up to assess durability of the device in patients who are expected to live longer than 2 years. Longer-term data will be collected in the PAS.

10.8.7 Days from Randomization to Procedure

In the TAVI group, there was a mean 11 day delay (median 7 days) from randomization to the procedure, whereas in the AVR group the mean was 16 days (median 9 days).

Because of the number of covariates, there is no statistical way to conclusively interpret these results. However, based on FDA's clinical interpretation, substantial delays between randomization and the procedure could have resulted in clinical status changes in the patients.

10.8.8 Procedure Data

The following table provides data on the procedures for patients in Cohort A. These data demonstrate that the TAVI procedure took, on average, over 4 hours and required general anesthesia in all patients. It is difficult to interpret the control AVR data since 13% of these patients had concomitant operations, such as other valve replacements, CABG, atrial fibrillation ablation, etc.

Table 30 - Procedure Data

Measured variable	TAVI (N=344)		AVR (N=313)
	Transapical (N=104)	Transfemoral (N=240)	
Total time in Cath Lab or OR in minutes (mean [min-max])	224.9 (93-595)	242.8 (0-624)	323.7 (0-750)
Skin to skin time in minutes (mean [min-max])	110 (9-514)	141 (32-510)	230.0 (169-295)
Fluoroscopy time in minutes (mean [min-max])	14 (5-60)	30 (7-121)	0 (0-0)
Volume of contrast in mL (mean [min-max])	104 (0-275)	148 (15-507)	0 (0-0)
Use of cannulation for cardiopulmonary bypass (n[%])	9/102 (8.8%)	5/234 (2.1%)	313/313 (100%)
Use of general anesthesia (n[%])	102/102 (100%)	240/240 (100%)	309/309 (100%)
# of devices used			
0 [n(%)]	3/102 (2.9%)	11/238 (4.6%)	N/A
1 [n(%)]	91/102 (89.2%)	216/238 (90.8%)	313/313 (100%)
2 [n(%)]	7/102 (6.9%)	10/238 (4.2%)	N/A
3 [n(%)]	1/102 (1.0%)	1/238 (0.4%)	N/A
More than one valve used [n(%)]	3/104 (2.9%)	4/240 (1.7%)	Na
Emergent operation due to device or procedure failure [n(%)]	1/104 (1.0%)	3/240 (1.3%)	12/313 (3.8%)
Valve size			
19 mm [n(%)]	N/A	N/A	37/312 (11.9%)
21 mm [n(%)]	N/A	N/A	124/312 (39.7%)
22 mm [n(%)]	N/A	N/A	1/312 (0.3%)
23 mm [n(%)]	52/101 (51.5%)	109/233 (46.8%)	109/312 (34.9%)
25 mm [n(%)]	N/A	N/A	37/312 (11.9%)
26 mm [n(%)]	49/101 (48.5%)	124/233 (53.3%)	N/A
27 mm [n(%)]	N/A	N/A	3/312 (1.0%)
29 mm [n(%)]	N/A	N/A	1/312 (0.3%)
Adverse event during procedure [n(%)]	20/102 (19.6%)	51/240 (21.3%)	46/313 (14.7%)

Results of interest are that all patients in the TAVI and AVR arms required general anesthesia. The total time in the procedure room was an hour less for TAVI patients than AVR patients, but the AVR arm includes patients with concomitant operations. Fluoroscopy time averaged 30-35 minutes, with a maximum time of over 2 hours, but no radiation dose data were collected in this study.

10.8.9 Cardiac Remodeling

The following parameters represent the echocardiographic markers for cardiac remodeling.

Table 31 - Echocardiographic Markers of Cardiac Remodeling

Parameter	Time	Pooled Control mean	Pooled SAPIEN mean
EF	Baseline	53.34	52.60
	1 yr	57.00	56.58
	delta	**+3.66**	**+3.98**
LVED volume	Baseline	119.05	123.34
	1 yr	102.10	114.15
	delta	**-16.95**	**-9.19**
LVES volume	Baseline	58.37	63.02
	1 yr	45.42	52.87
	delta	**-12.95**	**-10.15**
LV mass	Baseline	278.20	282.37
	1 yr	233.50	250.28
	delta	**-44.70**	**-32.09**

The parameters presented in the table above were selected because of the association with remodeling. There appears to be a slight numerical trend towards better LV remodeling with open AVR, but these differences are not clinically significant.

10.8.10 Aortic Valve Area

Aortic valve area was similar between the two groups at all time points where it was assessed.

10.8.11 Surgical Access for AVR and TAVI

The following table summarizes the data regarding the nature of the incisions used for open AVR and whether the patients were redo operations.

Table 32 - Prior Cardiac Surgery Stratified by Procedural Approach in AVR Patients (AT Population)

	Prior Open Heart Surgery (including CABG)		
	No	Yes	Total
AVR Full Sternotomy	128 (48.7%)	135 (51.3%)	263 (84.3%)
AVR Minimal Incision	45 (91.8%)	4 (8.2%)	49 (15.7%)
Total	173 (55.5%)	139 (44.6%)	312 (100.0%)

This indicates that about one third of the first-time surgical patients had minimally invasive approaches and that about three quarters of the TAVI patients required an open operation.

Patients with first time operations had higher rates of early (relative risk (RR) =2.1) and late (RR=1.5) death. Early (<30d) complications of stroke were higher (RR=2.2) in the redo group, but the late incidence of stroke was higher in the non-redo group. It is not clear if these results are independent of the procedure approach (full sternotomy versus minimal incision).

The following information was provided regarding how many patients needed an incision for direct arterial access versus a percutaneous puncture for arterial access.

Table 33 - Arterial Access for TAVI Procedures

Access Procedure	N (%)
Percutaneous catheter puncture only	66 (27.5%)
Incision for direct access Or Vascular operation after percutaneous access	171 (71.25%)
Missing information	3 (1.25%)

These data show that only about a quarter of the patients had only transcatheter insertion of the SAPIEN THV.

10.8.12 Explants

There were no explants in the AVR group. One Cohort A patient underwent surgical excision of the SAPIEN aortic bioprosthesis due to fungal endocarditis and underwent open AVR a year after SAPIEN placement.

10.8.13 More Than One Valve Used

Seven patients underwent procedures with more than one valve used. A brief description of these cases is included here:

i. Deployed in SAPIEN secondary to severe AI (patient died 10 days later)
ii. Deployed in SAPIEN secondary to severe AI
iii. Deployed in descending aorta after first valve in descending aorta
iv. Deployed in SAPIEN secondary to severe AI and 2 leaflets not working
v. First valve in descending aorta, second in "proper" position (Type B dissection)
vi. Hemodynamic collapse after first valve, second deployed.
vii. First valve in descending aorta, second in annulus

No preclinical testing has been conducted to support the safety of this procedure. This is significant given the potential for corrosion (fretting and galvanic) as well as other unknown risks associated with valve-in-valve implantation, such as long-term durability, valve migration/embolization, and access to the coronary ostia. Without any pre-clinical testing, and based on the limited clinical data available, it is difficult to draw conclusions regarding the short- and long-term safety of valve-in-valve implantation. Several risk mitigation measures, such as labeling, training, or requirements for additional testing may be appropriate in order to address this concern. At this time, the valve is indicated only for use in the native annulus.

10.8.14 Frailty as a Predictor of Short or Long-Term Mortality

Data regarding frailty was collected in two ways in order to determine a correlation of "frailty" with outcome. The first score was a qualitative assessment by the enrolling physician who was asked to answer "yes" or "no" as to whether the patient was frail. A total of 596 patients had this assessment. Frailty, as measured in this qualitative

assessment, did not correlate either with 30 day or mortality throughout the trial, therefore does not establish the relationship of frailty with outcome.

The sponsor later used a "frailty index" based on several criteria, including Activities of Daily Living, grip strength and 15-foot walk. These measurements were performed on 347 patients. The results did not correlate with either 30-day mortality or mortality over the length of the trial.

10.9 Sponsor Identified Secondary Endpoints

There were four pre-specified secondary endpoints associated with mathematical hypotheses. These data are presented in this section.

10.9.1 Major Adverse Cardiac and Cerebrovascular Events (MACCE) – Time from randomization to the first occurrence of a MACCE within 1 year

For the purposes of this analysis, MACCE includes all-cause death, myocardial infarction (MI), all stroke, and renal failure. These events have widely different clinical impact but they are treated as equal in this composite endpoint analysis. The KM event rates at 1 year are 26.6% and 27.4% for TAVI and AVR respectively for the AT population. The event rate difference (TAVI-AVR) is -0.8% with a two-sided 90% C.I. of (-6.6%, 4.9%).

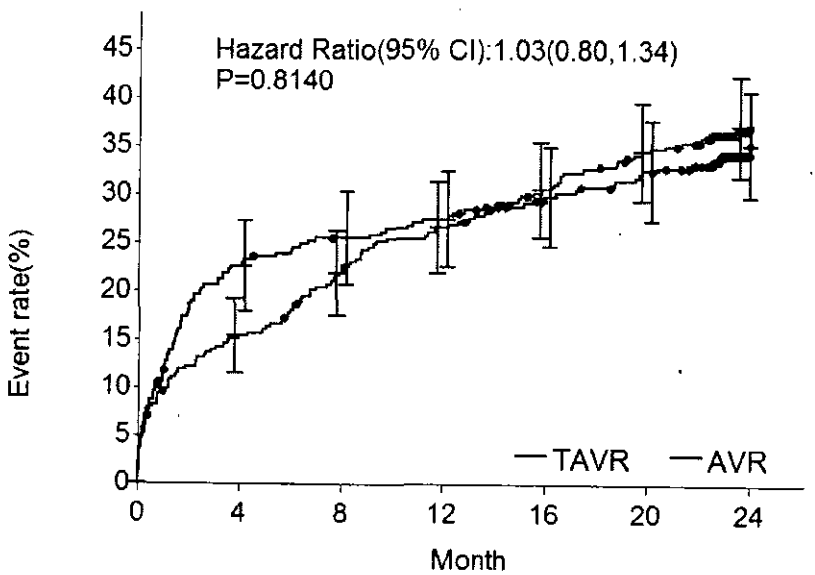


Figure 14 - First Occurrence of MACCE (AT Population)

Table 34 - MACCE Event at One Year in AT Population (using pre-specified adverse event definitions)

	Patients in group	Events	Patients with Event	KM Event rate at 1 Year
Death				
AVR	313	78	78	25.2%
TAVI	344	81	81	23.7%
Myocardial Infarction				
AVR	313	1	1	0.3%
TAVI	344	0	0	0.0%
Renal Failure				
AVR	313	11	10	3.5%
TAVI	344	7	7	2.1%
All Stroke				
AVR	313	9	9	3.0%
TAVI	344	19	19	5.8%
MACCE				
AVR	313	99	85	27.4%
TAVI	344	107	91	26.6%

The aforementioned interpretation limitations related to other analyses must also be considered in this analysis and interpretation of MACCE. Since the MACCE composite is not hierarchically weighted, it is important to examine each component adverse event, in particular, the almost 2-fold increase in the stroke rate. In addition, the definition of MACCE in this study does not include the important serious adverse events of vascular injury, hemorrhage, and aortic insufficiency.

10.9.2 Total Hospital Days to One Year Post-Procedure

In the ITT population, the mean number of hospital days through 1 year was 16.32 ± 18.0 days for the treatment group and 18.75 ± 22.58 days for the control. The median hospital stay days are 10 and 13 days for TAVI and AVR, respectively.

This analysis of hospital days is difficult to interpret because of the concomitant operations performed in the AVR group

10.9.3 New York Heart Association (NYHA) Class at One Year

For this parameter, when only in-window visit values were used, deleting all death (no imputation) and any missing for reasons other than death there are 251 patients in the test arm and 226 patients in the control arm included in the analysis.

There was a statistically significant difference in NYHA at 30 days, in favor of SAPIEN. Improvements of NYHA (as compared to baseline) at one year are shown in the following two tables for TAVI and AVR, respectively.

Table 35 - Cross Tabulation of NYHA Comparing Baseline and 1 Year in TAVI Patients (AT Population)

NYHA	1 Year						
Baseline	Class I	Class II	Class III	Class IV	Died	Missing	Total
Class I	0	0	0	0	0	0	0
Class II	7	4	1	0	6	2	20
Class III	54	43	12	1	29	5	144
Class IV	58	46	19	4	45	8	180
Died	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0
Total	119	93	32	5	80	15	344

Table 36 - Cross Tabulation of NYHA Comparing Baseline and 1 Year in AVR Patients (AT Population)

NYHA	1 Year						
Baseline	Class I	Class II	Class III	Class IV	Died	Missing	Total
Class I	0	0	0	0	0	0	0
Class II	6	3	2	0	3	2	16
Class III	47	42	9	1	30	5	134
Class IV	50	46	10	4	44	9	163
Died	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0
Total	103	91	21	5	77	16	313

The differences between the groups are clinically insignificant, however, the amount of missing data makes it problematic to draw any firm conclusions regarding these results.

10.9.4 Six Minute Walk Test (6MWT)

The 6 Minute Walk Test endpoint was added to the protocol after this unblinded study had started enrollment. Based on the available data from the test performed at 1 year, SAPIEN patients walked 164.96 ± 128.4 meters and control patients walked 69.84 ± 134.4 meters. Specifically, there are 198 patients in the test arm and 150 patients in the control arm included in the analysis.

The most important observation is that the above analysis was performed by including only in-window visit values, deleting all death (no imputation) and any missing for reasons other than death.

The significant amount of missing data makes it difficult to draw any firm conclusions regarding these results. There was minimal availability of paired data for the functional assessments. The setting of an unblinded trial further complicates the ability to draw conclusions from these data.

11. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

11.1 Continued Access Protocol (CAP) Cohort – Additional IDE Trial Data

The non-randomized Continued Access Protocol enrolled 843 transapical patients and 745 transfemoral patients. The following table shows that no patient has two events, so the numbers of patients with events and the number of events are the same.

Table 37 - All Cause Mortality - Randomized TAVI and CAP Patient by Implant Approach (ITT Population)

		≤ 30 Days			31 Days – 1 Year		
	Patients in Group	Events	Patients with Event	KM Event rate at 30 Days	Events	Patients with Event	KM Event rate at 1 Year
Death							
CAP - TA	843	57	57	7.0%	93	93	24.1%
Randomized TAVR - TA	104	4	4	3.8%	26	26	29.0%
CAP - TF	745	24	24	3.3%	83	83	20.6%
Randomized TAVR - TF	244	8	8	3.3%	46	46	22.2%

For stroke, the number of events does not always match the number of patients; some patients had more than one event.

Table 38 - Stroke - Randomized TAVI and CAP Patient by Implant Approach (ITT Population)

		≤ 30 Days			31 Days – 1 Year		
	Patients in Group	Events	Patients with Event	KM Event rate at 30 Days	Events	Patients with Event	KM Event rate at 1 Year
Stroke							
CAP –TA	843	17	16	2.0%	6	6	3.7%
Randomized TAVR – TA	104	6	6	5.8%	3	3	9.6%
CAP TF	745	29	28	3.9%	10	10	5.8%
Randomized TAVR - TF	244	10	10	4.1%	1	1	4.6%

11.1.2 Summary of Data Outside of the U.S. IDE Study

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 a 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 39 - 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 40 - 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-predict risk by as much as a factor of three.[5,6]

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" or high risk 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.

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

12.1 Panel Meeting Recommendation

An advisory meeting of the Circulatory System Devices Panel was held on June 13, 2012, at which three questions were held for a vote. The outcome of the votes was as follows:

Question 1
The panel voted 10-2 that the data shows reasonable assurance that the Edwards SAPIEN™ Transcatheter Heart Valve is safe for use in patients who meet the criteria specified in the proposed indication.

Question 2
The panel voted 12-0 that there is reasonable assurance that the Edwards SAPIEN™ Transcatheter Heart Valve is effective for use in patients who meet the criteria specified in the proposed indication.

Question 3
The panel voted 11-0 (with one abstaining) that the benefits of the Edwards SAPIEN™ Transcatheter Heart Valve do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

The Panel further recommended refinements to the physician and patient labeling, and that a refined Post Approval Study be conducted. Their recommendations are summarized below:

(1) Refinements to the Instructions for Use (IFU) to limit use in patients with severe symptomatic calcified native aortic valve stenosis.

(2) Refinements to the rest of the IFU including addition of a warning statements regarding lack of data for use of valve-in-valve technique; noting results of sub-group analyses (gender analysis, transfemoral versus transapical performance) in the Clinical Experience section of the IFU; noting results of aortic regurgitation and stroke in the Clinical Experience section of the IFU; listing important criteria used for determining high risk status; providing guidance on sizing of the annulus and valve in the IFU; noting the pros and cons for both AVR and TAVI in the label; and noting that AVR is an alternative to TAVI;

(3) Refinements to the patient label, especially in the area of stroke risk and gender differences;

(4) Recommendation for protocols for two post-approval studies:

- follow-up of patients enrolled in the IDE out to 5 years, and

- newly implanted subjects to evaluate learning curve, anticoagulation, and adverse events compared to those seen in the IDE study. The Panel recommended gathering additional supporting data on: stroke (with a neurologist added to the team and a possible subset of subject assessed using diffusion weighted MRI, in addition to modified Rankin Scale and NIHSS); atrial fibrillation and its association to mortality; longer term echocardiograms to evaluate aortic regurgitation (separated by mild versus moderate and severe); vascular complications; anesthesia use; hospital stay; cause of death; and a range of antithrombotic therapies; and hypothesis-driven gender assessments using propensity scores.

(5) Additional details and data collection regarding the frailty assessments and data.

12.2. FDA's Post-Panel Action

FDA agreed with all of the panel suggestions and 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.

13. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

13.1 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. The durability of the valve when used in "valve-in-valve" applications was not assessed in pre-clinical studies.

In this high risk population, there was no statistical difference in 1-year survival between TAVI and open AVR. Female patients did somewhat better with the TAVI transfemoral approach versus open AVR, while male patients with the transfemoral approach did better with open surgery. Transapical patients did better with open surgery than with TAVI. The TAVI procedure results in one half the amount of bleeding than the open surgical procedure. However, there was a doubling in the incidence of stroke in the TAVI cohort (5.5 vs. 2.9%); there was a four-fold increase in the incidence of aortic regurgitation in the TAVI cohort (74.4% vs. 21.8%); and there was a three-fold increase in vascular complications in the TAVI cohort (11.0% vs. 3.8%). Stroke, regurgitation and vascular complications have long-term effects on patient quality of life.

There were a number of factors in the randomized study that may have confounded the analysis of the data or created bias. In addition, even though the stroke rate in the TAVI group was higher than in the AVR group in the randomized study, there was a trend toward improvement in the rate in the CAP study. Improvements continued throughout the study with regard to delivery device design, patient enrollment criteria, and training of users and these measures appear to have had a positive effect on outcome.

In conclusion, for patients who are at high risk for mortality from surgery, TAVI provides an alternative to correcting aortic valve stenosis. Possible risks should be weighed against the benefits.

13.2 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.

13.3 Benefit-Risk Conclusions

The probable benefits of the SAPIEN THV TAVI procedure are also based on data collected in a clinical study conducted to support PMA approval as described above.

The benefit of SAPIEN THV implantation is that it is a reasonable alternative for patients who are too high risk to undergo surgical replacement of their stenotic aortic valve. The trial met its primary endpoint of similar one year mortality between the control and treatment groups. More specifically, mortality was similar at 30 days, 1 year and 2 years. In addition, there was similar improvement in symptoms presumably due to the similar increase in aortic valve area produced by both treatments. Other benefits include improved overall hemodynamic performance, improved quality of life in the acute phase, slightly better outcome in women compared with open surgery, and less bleeding than with open surgery.

There is an early peri-procedural increased risk of stroke with SAPIEN THV that does not appear to substantially increase over time. SAPIEN THV is also associated with an increased risk of major vascular complications while cardiac surgery is associated with an increased risk of major vascular bleeding. Lastly, mild perivalvular regurgitation appears associated with increased late mortality.

Longer-term data indicate that the composite endpoint of mortality or stroke is similar between TAVI and cardiac surgery at one and two years. Additional continued access protocol data as well as the world wide SAPIEN THV experience indicate that rates of stroke, major vascular complications and major bleeding are improving as more experience accumulates with this procedure.

Additional factors to be considered in determining probable risks and benefits for the SAPIEN THV include carefully reviewing the limitations of data interpretation due to confounding factors such as missing data and variations in patient selection, site enrollment and individual patient treatment. Patient comorbidities (particularly those excluded from the study) and patient anatomic characteristics (especially those excluded from this study) should also be considered in evaluating these data.

The net sum of these results indicates an appropriate benefit to risk profile so that from a patient's perspective TAVI is a reasonable alternative to standard cardiac surgical valve replacement in this high-risk aortic stenosis population. Recommendations to individual patients need to balance the appeal of avoiding open-heart surgery with the known

increased peri-procedural risks of TAVI, particularly with regards to stroke. An informative dialogue between the patient and their heart team (cardiologist and surgeon) is therefore critical for individual patient decision making.

In conclusion, given the available information above, the data support that for patients at high risk of mortality from open surgery, the probable benefits outweigh the probable risks.

13.4 Overall Conclusions

The Edwards Partner Cohort A randomized control trial compared TAVI to standard cardiac surgery in selected high-risk patients with aortic stenosis. 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 implantation of the SAPIEN THV in the native aortic calcified annulus in symptomatic, high risk patients.

14. CDRH DECISION

FDA issued an approval order on October 19, 2012. 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 protocol dated May 2012 Version 5.1, located in PMA Amendment 12. The study will consist of All IDE patients currently enrolled and alive. 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: KCCQ, SF-12, and EQ-5D Utilities. The surviving patients in the premarket cohort at the time of PMA approval will be followed annually up to five-years.

2. Newly Enrolled Study: This study should be conducted as per protocol dated June 2012 Version 1.1, located in PMA Amendment 14. This study will consist of a minimum of 700 patients for high risk Transfemoral patients, and a minimum of 1010 patients for high risk Transapical patients in 35 sites. Sites will be selected to ensure that large volume (>200 valves per year), medium volume (100□200 valves per year) and small volume (50□100 valves per year) are represented in the analysis.

   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, and (3) composite safety and effectiveness endpoints at 30 days and annually through five years post-implant.

   For the transfemoral approach, the 30 day and one year evaluation of stroke requires a sample size of 564 and 614 respectively assuming a the background incidence risk of 3.75% and 4.17% respectively in order to detect an increase of 0.03.

   For the transapical approach, the 30 day and one year evaluation of stroke requires a sample size of 916 and 730 respectively assuming a the background incidence risk of

6.73% and 9.62% respectively in order to detect an increase of 0.03 and 0.04 respectively.

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

15. 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.

16. REFERENCES

[1] Moat NE, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J Am Coll Cardiol 2011; 58:2130-2138.

[2] Gotzmann M, et al. Transcatheter aortic valve implantation in patients with severe symptomatic aortic valve stenosis-predictors of mortality and poor treatment response. Am Heart J 2011; 162:238.e1-245.e1.

[3] Gilard M, et al. Registry of Transcatheter Aortic-Valve Implantation in High-Risk Patients. N Engl J Med 2012;366:1705-1715.

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[5] 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.

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