SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Aortic valve, prosthesis, percutaneously delivered

Device Trade Name: Edwards SAPIEN XT™ Transcatheter Heart Valve, model 9300TFX, 23, 26, and 29 mm, and accessories
(NovaFlex+ delivery system, models 9355FS23, 9355FS26, and 9355FS29, with crimp stopper and Qualcrimp crimping accessory (laminated model or cloth model 9300QC);
Edwards Expandable Introducer Sheath Set, models 916ES23, 918ES26, and 920ES29;
Edwards balloon catheter, models 9350BC20, 9350BC23, and 9350BC25;
Ascendra+ delivery system with crimp stopper, models 9355AS23, 9355AS26, and 9355AS29;
Ascendra+ introducer sheath set, models 9350IS23, 9350IS26, and 9350IS29;
Ascendra balloon aortic valvuloplasty catheter, model 9100BAVC; and Edwards crimper, model 9350CR)

Device Procode: NPT

Applicant's Name and Address: Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614

Date(s) of Panel Recommendation: None

Premarket Approval (PMA) Application Number: P130009

Date of FDA Notice of Approval: June 16, 2014

II. INDICATIONS FOR USE

The Edwards SAPIEN XT Transcatheter Heart Valve, model 9300TFX, and accessories are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 cm^2/m^2, a mean aortic valve gradient of ≥ 40 mmHg, or a peak aortic-jet velocity of ≥ 4.0 m/s), and with native anatomy appropriate for the 23, 26, or 29 mm valve system, who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score $\geq$8% or at a $\geq$15% risk of mortality at 30 days).

III. CONTRAINDICATIONS

The transcatheter heart valve (THV) and delivery systems are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions can be found in the Edwards SAPIEN XT THV labeling.

V. DEVICE DESCRIPTION

The Edwards SAPIEN XT THV, shown in **Figure 1**, is comprised of a balloon-expandable, radiopaque, cobalt chromium frame, trileaflet bovine pericardial tissue valve and polyethylene terephthalate (PET) fabric skirt. The leaflets are treated according to the Edwards ThermaFix™ process, and the valve is packaged and terminally sterilized in glutaraldehyde.

23mm and 26mm **29mm**

Figure 1: SAPIEN XT Transcatheter Heart Valve

The NovaFlex+ delivery system, shown in **Figure 2**, includes a handle that provides a flex wheel for articulation of the flex catheter, a tapered tip at the distal end of the delivery system to facilitate crossing the native valve, a balloon catheter for deployment of the THV, and radiopaque markers.

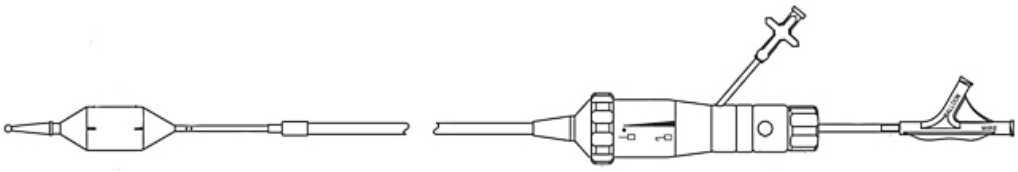

Figure 2: NovaFlex+ Delivery System

The Edwards Expandable Introducer Sheath Set, shown in **Figure 3**, consists of a sheath, introducer, and loader.

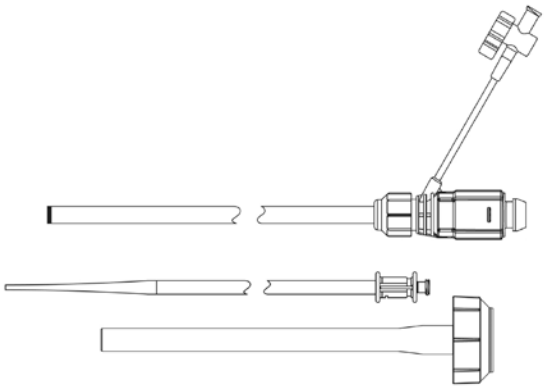

Figure 3: Edwards Expandable Introducer Sheath Set

The Edwards balloon catheter, shown in **Figure 4**, consists of a balloon, radiopaque marker bands, guidewire shaft, balloon catheter shaft, strain relief, and Y-connector.

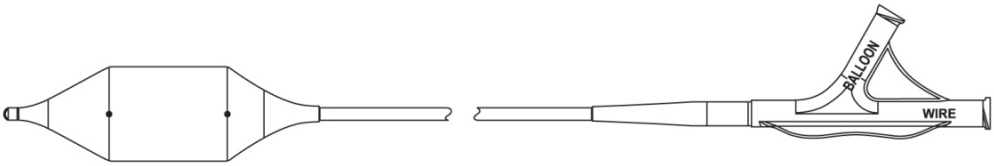

Figure 4: Edwards Balloon Catheter

The Qualcrimp crimping accessory, shown in **Figure 5**, is a non patient-contacting device that is placed around the Edwards SAPIEN XT THV to protect the leaflets during the crimping process. It is available in two models. The cloth model is manufactured from ester-based polyurethane compressed foam encapsulated in a single piece of knitted polyester cloth that is wrapped around the foam and sutured at the top. The laminated model is manufactured of tubular polyester polyurethane foam that is laminated cylindrically on both the inner and outer surfaces with a polyether urethane material.

Cloth Model Laminated Model

Figure 5: Qualcrimp Crimping Accessory

The Ascendra+ delivery system, shown in **Figure 6**, has radiopaque markers for visualization under fluoroscopy, a balloon for deployment of the THV and a handle. The system comes with a loader that is used to cover the THV during delivery. An extension tube is supplied for use with the delivery system during inflation.

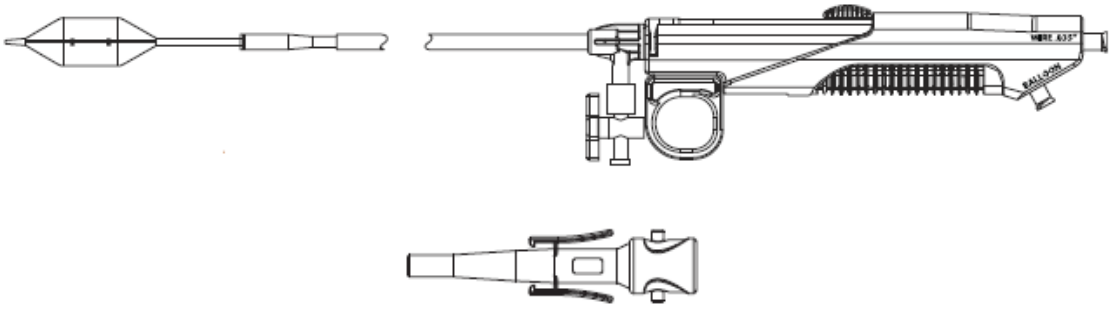

Figure 6: Ascendra+ Delivery System

The Ascendra+ introducer sheath set, shown in **Figure 7**, consists of an introducer and sheath.

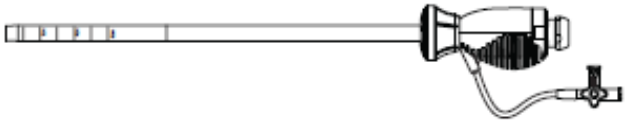

Figure 7: Ascendra+ Introducer Sheath Set

The Ascendra balloon aortic valvuloplasty catheter, shown in **Figure 8**, 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 aortic valvuloplasty catheter is supplied with optional extension tubing.

Figure 8: Ascendra Balloon Aortic Valvuloplasty Catheter

The Edwards crimper, shown in **Figure 9**, is comprised of various molded plastic components which compress the valve to a controlled aperture. The aperture is created by rotating the handle until it abuts the crimp stopper. The Edwards crimper includes a 2-piece crimp stopper (packaged with the NovaFlex+ delivery system) or a one-piece crimp stopper (packaged with the Ascendra+ delivery system) used to correctly crimp the THV.

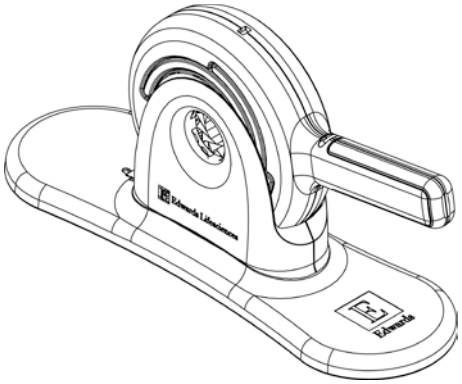

Figure 9: Edwards Crimper

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for patients with severe symptomatic native aortic valve stenosis deemed to be non-operable (non-surgical), including treatment with other commercially available transcatheter aortic valve replacement (TAVR) devices, temporary relief using percutaneous balloon aortic valvuloplasty (BAV) or medical therapy (non obstruction-relieving intervention). For patients who are deemed operable, but at high risk, surgical aortic valve replacement (SAVR) or replacement with other commercially available TAVR devices are alternatives. 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 his/her needs.

VII. MARKETING HISTORY

Commercial distribution of the SAPIEN XT THV, model 9300TFX, and accessories outside the U.S. began in March 2010. Currently, the device is approved in the 28 member states under the European Union (i.e., Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom) and other countries, including Azerbaijan, Belarus, Bosnia and Herzegonia, Brazil, Canada, Columbia, Egypt, Georgia, Iceland, Iran, Israel, Japan, Jordan, Korea, Kuwait, Lebanon, Maghreb, Moldova, Monaco, Montenegro, Norway, Oman, Russia, Saudi Arabia, South Africa, Switzerland, Turkey, United Arab Emirates, and Venezuela. The device is also commercially distributed in compliance with applicable local requirements in Chile and New Zealand.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The adverse effects listed below are associated with access complications relating to catheterization or valvuloplasty and local and/or general anesthesia:

- Death
- Stroke/transient ischemic attack, clusters or neurological deficit
- Paralysis

- Permanent disability
- Respiratory insufficiency or respiratory failure
- Hemorrhage requiring transfusion or intervention
- Cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention
- Pericardial effusion or cardiac tamponade
- Embolization including air, calcific valve material or thrombus
- Infection including septicemia and endocarditis
- Heart failure
- Myocardial infarction
- Renal insufficiency or renal failure
- Conduction system 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, contrast media, or device materials
- Hematoma
- Syncope
- Pain or changes at the access site
- Exercise intolerance or weakness
- Inflammation
- Angina
- Heart murmur
- Fever

Additional potential risks associated with the use of the THV, delivery system and/or accessories include:

- 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, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis)
- Device degeneration
- Paravalvular or transvalvular leak
- Valve regurgitation
- Hemolysis
- Device explants
- Nonstructural dysfunction
- Mechanical failure of delivery system, and/or accessories
- Non-emergent reoperation

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

In vitro studies were performed on the Edwards SAPIEN XT THV, model 9300TFX, and non-implantable accessories. Valve testing was performed in conformity with FDA's *Draft Replacement Heart Valve Guidance* (1994) and ISO 5840: *Cardiovascular Implants-Cardiac Valve Prostheses* (2005).

1. Biocompatibility Studies

Toxicology and biocompatibility testing for the SAPIEN XT THV, model 9300TFX, and accessories was conducted in accordance with ISO 10993-1: *Biological Evaluation of Medical Devices Part 1: Evaluation and Testing*. Summaries of the test results for the SAPIEN XT THV, NovaFlex+ delivery system, Ascendra+ delivery system, Edwards Expandable Introducer Sheath Set, Ascendra+ introducer sheath set, Edwards balloon catheter, Ascendra balloon aortic valvuloplasty catheter, Qualcrimp crimping accessories (cloth model and laminated model), and Edwards crimper are provided in **Tables 1-6**. 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 acceptable.

Table 1: Summary of Biocompatibility Testing – SAPIEN XT THV (Model 9300TFX)

Test	Purpose	Results
Cytotoxicity: Percent Inhibition of Cell Growth	Determine whether test article extract would inhibit cell growth.	Test article found to be non-inhibitory to cell growth at a sample concentration representative of the device's clinical application. Inhibitory to cell growth at elevated sample concentrations.
Cytotoxicity: Medium Eluate Method (MEM)	Determine whether test article extracts would cause cytotoxicity and cell lysis	Test article sample was non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control.
Cytotoxicity: Agar Overlay Test	Determine whether solid samples of test article would cause cytotoxicity and cell lysis.	Solid samples of the stent frame were non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control. Cytotoxicity was observed in solid samples of the cloth, suture, and tissue material due to glutaraldehyde and formaldehyde residuals present in the solid sample.
Sensitization: Guinea Pig Maximization	Investigate the potential for delayed dermal contact sensitization.	No irritation was present on any of the test or control animals at 24 or 48 hour readings using saline and vegetable oil extracts. Non-sensitizing.
Irritation/Intracutaneous Toxicity: Rabbit Intracutaneous Reactivity	Determine whether test article extracts would cause local dermal irritation or toxic effects.	No evidence of irritation or abnormal effects over a 72 hour period as compared to negative controls.
Systemic Toxicity: USP Mouse Systemic Injection	Determine whether test article extracts would cause acute systemic toxicity.	No weight differences or observed systemic effects as compared to negative controls over 72 hour test period.
Systemic Toxicity: Material Mediated (Rabbit) Pyrogen Test	Determine the presence of chemical pyrogens in test article extracts by measuring temperature rise in intravenously injected rabbits.	Temperature rise of $\leq 0.5°C$ and no 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. typhimuruim* 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.

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

Table 2: Summary of Biocompatibility Testing – NovaFlex+ Delivery System, Edwards Balloon Catheter and Ascendra+ Delivery System, and Ascendra Balloon Aortic Valvuloplasty Catheter

Test	Purpose	Results
Cytotoxicity: Medium Eluate Method (MEM)	Determine whether test article extracts would cause cytotoxicity and cell lysis	Test article sample was non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control.
Cytotoxicity: Agar Overlay Test	Determine whether solid samples of test article would cause cytotoxicity and cell lysis	Solid samples of test articles were non-cytotoxic. 0% cell lysis was observed with equivalent results to the negative control.
Sensitization: Guinea Pig Maximization	Investigate the potential for delayed dermal contact sensitization	No irritation was present on any of the test or control animals at 24 and 48 hour readings using saline and vegetable oil extracts (additional 72 hours readings were performed for NovaFlex+). 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: Mouse Systemic Injection	Determine whether test article extracts would cause acute systemic toxicity	No weight differences or observed systemic effects as compared to negative controls over 72 hour test period.
Systemic Toxicity: Material Mediated (Rabbit) Pyrogen Test	Determine the presence of chemical pyrogens in test article extracts by measuring temperature rise in intravenously injected rabbits.	Temperature rise of $\leq 0.5°C$ and no abnormalities in any test or control animals.
Hemocompatibility: Hemolysis	Determine whether the test article would cause hemolysis 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 – Edwards Expandable Introducer Sheath Set 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.
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 hour 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 as compared to negative controls. Non-irritating.
Systemic Toxicity: Mouse Systemic Injection	Determine whether test article extracts would cause acute systemic toxicity	No significant systemic effects observed as compared to negative controls. Systemically non-toxic.
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. Systemically non-toxic.
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 4: Summary of Biocompatibility Testing – Qualcrimp Crimping Accessory (Cloth Model)

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

Table 5: Summary of Biocompatibility Testing – Qualcrimp Crimping Accessory (Laminated Model)

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.

Table 6: Summary of Biocompatibility Testing – Edwards Crimper (Model 9350CR)

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.
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.

2. SAPIEN XT THV Hydrodynamic Performance

In vitro hydrodynamic performance studies of the SAPIEN XT 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 (i.e., under deployed, oval deployed, and over deployed). The studies were conducted in accordance with FDA's *Draft Replacement Heart Valve Guidance* (1994) and/or ISO 5840: *Cardiovascular Implants-Cardiac Valve Prostheses* (2005). Reference articles for the nominally deployed SAPIEN XT valve studies consisted of commercially available aortic valves; reference articles for the irregular studies consisted of nominally deployed SAPIEN XT valves. A matrix of the tests performed and corresponding results is provided in **Table 7**.

Table 7: 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: SAPIEN XT Size 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, & surgical Perimount Magna size 23mm, 27mm & 29mm valves; reference nozzle Irregular Test: Irregular SAPIEN XT size 23mm, 26mm & 29mm	The SAPIEN XT valve offers acceptable hemodynamics with pressure gradients and effective orifice areas (EOA) that are comparable to those offered by the reference valves.

Test	Purpose/Objective	Test/Reference Articles	Results
		Reference: Nominal SAPIEN XT size 23mm, 26mm & 29mm; Nominal SAPIEN size 23mm & 26mm; reference nozzle	
Steady Backflow Leakage	To determine the leakage rate at various steady back flow pressures.	<u>Nominal</u> Test: SAPIEN XT Size 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, & surgical Perimount Magna size 23mm, 27mm & 29mm valves; reference nozzle <u>Irregular</u> Test: Irregular SAPIEN XT size 23mm, 26mm & 29mm Reference: Nominal SAPIEN XT size 23mm, 26mm & 29mm; Nominal SAPIEN size 23mm & 26mm; reference nozzle	The SAPIEN XT valve offers satisfactory performance in terms of its competency to prevent significant transvalvular aortic back-flow during the diastolic phase.
Pulsatile Flow Pressure Drop	To determine pressure drop and effective orifice area performance under pulsatile flow conditions.	<u>Nominal</u> Test: SAPIEN XT Size 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, & surgical Perimount Magna size 23mm, 27mm & 29mm valves <u>Irregular</u> Test: Irregular SAPIEN XT size 23mm, 26mm & 29mm Reference: Nominal SAPIEN XT size 23mm, 26mm & 29mm; Nominal SAPIEN size 23mm & 26mm	The SAPIEN XT 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.	<u>Nominal</u> Test: SAPIEN XT Size 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, & surgical Perimount Magna size 23mm, 27mm & 29mm valves <u>Irregular</u> Test: Irregular SAPIEN XT size 23mm, 26mm & 29mm Reference: Nominal SAPIEN XT size 23mm, 26mm & 29mm;	The SAPIEN XT valve offers acceptable hydrodynamics with regurgitant fractions that were lower than those required by the ISO 5840:2005 acceptance criteria.

Test	Purpose/Objective	Test/Reference Articles	Results
		Nominal SAPIEN size 23mm & 26mm	
Flow Visualization	To qualitatively investigate flow characteristics in the vicinity of the valve.	Nominal Test: SAPIEN XT Size 23mm Reference: SAPIEN size 23mm Irregular Test: Irregular SAPIEN XT, sizes 23mm & 29mm Reference: Nominal SAPIEN XT size 23mm & 29mm	The SAPIEN XT valve offers acceptable aortic flow patterns throughout the entire cardiac cycle. Broad central jet-like flows with no flow stasis during opening were observed in all SAPIEN XT 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: SAPIEN XT Size 23mm, 26mm & 29mm Irregular Test: Irregular SAPIEN XT Size 23mm, 26mm & 29mm Reference: Nominal SAPIEN XT size 29mm	Pressure drop results for the SAPIEN XT valve demonstrated correlation with the Bernoulli relationship.

3. SAPIEN XT THV Structural Performance

In vitro structural performance studies of the SAPIEN XT THV were performed. The studies were conducted in accordance with FDA's *Draft Replacement Heart Valve Guidance* (1994) and/or ISO 5840: *Cardiovascular Implants-Cardiac Valve Prostheses* (2005). Commercially available bioprosthetic aortic valves 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 8**.

Table 8: 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: SAPIEN XT size 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, & surgical Perimount Magna size 23mm, 27mm & 29mm valves Irregular Test: SAPIEN XT size 23mm, 26mm & 29mm Reference: PERIMOUNT size 23mm, 27mm & 29mm; Nominal	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.

Test	Purpose/Objective	Test/Reference Articles	Results
		SAPIEN XT size 23mm and 26mm	
Dynamic Failure Mode	To obtain information about the failure modes affecting the durability of the valve.	Test: SAPIEN XT size 23mm, 26mm & 29mm Reference: PERIMOUNT Size 23mm, 27mm & 29mm	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 XT frames size 23mm, 26mm & 29mm	Minimum force required to compress the frame was acceptable.
Frame Corrosion Resistance	To characterize the corrosion resistance of the valve frames and 4-hole bars in accordance with ASTMF2129-08	Test: SAPIEN XT frames size 23mm, 26mm & 29mm, SAPIEN XT 4-hole bars Reference: Cordis Palmaz Genesis stents	Corrosion resistance of SAPIEN XT cobalt chromium frames and 4-Hole Bars are equivalent to the commercially available stent.
Frame Fatigue	To determine frame fatigue resistance to 600 million cycles.	Test: SAPIEN XT frames size 23mm, 26mm & 29mm	No frame cracks or fractures were observed at 10x magnification following 600 million cycles of fatigue testing.
Stress Analysis (FEA)	To characterize mechanical behavior of the frame during deployment and operation.	Modeling based on *in vitro* and clinical data of 23mm, 26mm & 29mm SAPIEN XT frames.	Results indicate that the worst-case 26mm & 29mm SAPIEN XT frame should not fracture for 600 million cycles, even under the unlikely simultaneous combination of all the worst-case conditions.

4. SAPIEN XT THV Design Specific Performance Studies

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

5. SAPIEN XT THV Magnetic Resonance Imaging (MRI) Compatibility

Testing of the size 23 mm, 26 mm, and 29 mm frames in magnetic fields of 1.5 and 3.0 Tesla has shown that the SAPIEN XT THV is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla or 3.0 Tesla
- Spatial gradient field of 2500 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (WB-SAR) of 2.0 W/kg for 15 minutes of scanning.
- Normal mode operation, as defined in IEC 60601-2-33, of the MR system

6. Delivery System and Accessory Performance Testing

The following tests were performed for the NovaFlex+ delivery system and the Ascendra+ delivery system and showed acceptable results: dimensional verification, visual inspection, simulated use, balloon characterization, bond strength, and hemostasis. The NovaFlex+ delivery system was also subjected to valve retention testing.

The following tests were performed for the Edwards Expandable Introducer Sheath Set and 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 Edwards balloon catheter and 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 Qualcrimp and showed acceptable results: dimensional verification, visual inspection, and simulated use.

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

7. Sterilization

The SAPIEN XT THV is sterilized by terminal liquid sterilization (TLS) in buffered glutaraldehyde solution. The NovaFlex+ delivery system, Ascendra+ delivery system, Edwards Expandable Introducer Sheath Set, Ascendra+ introducer sheath set, Edwards balloon catheter, Ascendra balloon aortic valvuloplasty catheter, Qualcrimp crimping accessory, and Edwards 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) of 10^{-6} in validation studies.

8. 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 NovaFlex+ delivery system, Ascendra+ delivery system, Edwards Expandable Introducer Sheath Set, Ascendra+ introducer sheath set, Edwards balloon catheter, Ascendra balloon aortic valvuloplasty catheter, Qualcrimp, and Edwards crimper.

The 23mm and 26mm SAPIEN XT THVs are labeled with a two (2) year shelf life; the 29mm SAPIEN XT THV is currently labeled with a one (1) year shelf life.

9. Package Integrity

The packaging for the SAPIEN XT THV 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 five years of real-time aging and exposure to temperature variations and simulated shipping conditions.

The NovaFlex+ delivery system, Ascendra+ delivery system, Edwards Expandable Introducer Sheath Set, Ascendra+ introducer sheath set, Edwards balloon catheter, Ascendra balloon aortic valvuloplasty catheter, Qualcrimp crimping accessory, and Edwards 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.

10. Product Integrity

SAPIEN XT THV Biological Tissue
Edwards ThermaFix-processed bovine pericardial tissue has previously been validated and approved under PMA P860057 regarding the Carpentier-Edwards® PERIMOUNT® Pericardial Bioprosthesis product family, and PMA P100041 and P110021 for the SAPIEN THV. The tissue used for the SAPIEN XT THV is identical to the tissue used in the PERIMOUNT and SAPIEN valves. Biochemical evaluation was conducted on tissue stored in glutaraldehyde solution for four years of real time aging. 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 XT THV. A stress relaxation study was completed to compare cyclic load decay for tissue leaflet samples at zero-time to tissue leaflets after three years of real-time aging. No statistically significant difference was observed between the two groups.

SAPIEN XT THV Non-biological Components and Whole Valve Testing
Functionality of the SAPIEN XT THV's non-biologic components (polymers: valve holder, skirt, sleeve, and sutures; and metallics: frame) and whole-valve hydrodynamic and wear testing were completed after 2 years of real-time aging (for size 23 and 26mm valves).

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 XT THVs (sizes 23mm and 26mm) 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. The size 29 mm SAPIEN XT is currently labeled with a 1 year shelf life, which was substantiated based on in vitro testing of real time aged tissue and non-biologic components, as noted above.

Delivery System and Accessories

Functionality and product integrity of the NovaFlex+ delivery system, Ascendra+ delivery system, Edwards Expandable Introducer Sheath Set, Ascendra+ introducer sheath set, Edwards balloon catheter, Ascendra balloon aortic valvuloplasty catheter, Qualcrimp crimping accessory, and Edwards crimper was demonstrated after two years of accelerated aging, exposure to temperature variations and simulated shipping conditions.

B. SAPIEN XT THV Animal Studies

A chronic study was performed on the SAPIEN XT THV using 37 young adult male sheep implanted with annuloplasty rings in the aortic annulus to model the semi-rigid environment of the diseased aortic root found in the stenotic clinical situation. The THVs were surgically implanted, but deployed using a delivery system for simulated use. The study used the smallest size (23 mm) SAPIEN XT THVs due to anatomical limitations of the animal model. The endpoints of the animal study are a function of valve design and material interactions, and therefore the results of the study are applicable to all valve sizes. An overview of the study is provided in **Table 9**.

Table 9: GLP Chronic Study Overview

Sample Size/Animal Model	37 young adult male sheep Annuloplasty rings were surgically implanted into the aortic annulus to model the semi-rigid environment of the diseased aortic root found in the stenotic clinical situation.
Test Articles	Size 23 mm SAPIEN XT transcatheter heart valve, model 9300TFX.
Control Articles	Commercially available SAPIEN transcatheter heart valve (model 9000TFX) and Carpentier-Edwards PERIMOUNT pericardial bioprosthesis (model 2800TFX).

Technique	Transcatheter heart valves were surgically implanted into the annuloplasty rings using the delivery system for simulated use. The Carpentier-Edwards PERIMOUNT valves were surgically implanted per directions for use.
Results	37 implants attempted 34 implanted with either SAPIEN XT or SAPIEN transcatheter heart valves; 3 with PERIMOUNT surgical valves 20 successful animals (sacrificed between 10 - 20 weeks) 16 early deaths 15 non-related early deaths 1 procedure related death
Conclusion	14 animals survived to 20 weeks (six 9300TFX test valves, six 9000TFX control valves, and 2 2800TFX control valves). The gross findings and histopathology results suggest that the valve is capable of long-term implant.

A total of 34 SAPIEN XT and SAPIEN THVs were implanted for a 10 week and 20 week evaluation study: 6 animals (three SAPIEN XT and three SAPIEN) were electively sacrificed at 10 weeks, and 12 (six SAPIEN XT and six SAPIEN) survived to 20 weeks. Three (3) model 2800TFX surgical control articles were implanted in the aortic position of 3 adult male sheep: 2 survived to 20 weeks and were clinically normal prior to explant; 1 survived less than 14 days. The results of this study demonstrated that the SAPIEN XT THV has acceptable hemodynamic performance and is suitable for long-term implant. The three valve models were comparable for all parameters evaluated. A summary of the study results is provided in **Table 10**.

Table 10: GLP Chronic Study Summary

Evaluation Parameter	Summary of Results
Clinical History and Hematology	All six 10-week and thirteen of the fourteen 20-week sheep were clinically normal prior to explants. One animal experienced an increased respiratory rate and effort two weeks post operative and remained on diuretic therapy until sacrifice. Clinical chemistry and complete blood count results were within normal limits for the majority of animals at implant and explant. Five animals, from test and control groups, showed moderately low platelet count. Among the remaining animals, some values were either slightly above or below the reported normal range but none was considered to clinically significant. Findings were comparable between all groups. None of the pre-implant and pre-explant abnormal hematology findings were considered to be clinically significant to affect the outcome of the study.
Hemodynamic Performance	In general, peak gradients and cardiac outputs at explants tended to be higher than at implant. The 9300TFX and 9000TFX valves had evidence of valvular insufficiency by contrast angiography. The gaps were located between the annuloplasty ring and the aortic wall and were a failure of the model and not a problem with the valve delivery or performance. One 2800TFX control valve had paravalvular gap from possible suture tear. Angiography evaluation at 20 weeks indicated that 5 of 6 test valves had grade 1-2 regurgitation and 1 of 6 had grade 3-4 regurgitation. For the 9000TFX control valve

Evaluation Parameter	Summary of Results
	at 20 weeks, 4 of 6 had grade 1-2 regurgitation and 2 of 6 had grade 3-4 regurgitation. For the 2800TFX control valve at 20 weeks, 1 of 2 had grade 3-4 regurgitation and 1 of 2 had no evidence of regurgitation.
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 three valve models at 20 weeks. There were no thrombus, valvular mineralization and vegetative growths in 17 of 18 valves. There was no migration, leaflet damage, material wear, or structural failure in 17 of 18 valves. Minimal thrombus formation with unknown etiology was observed in the inflow aspect and minimal leaflet transparency observed on the outflow aspect of a model 9300TFX; attributable to compression lines caused by valve crimping. All valves showed no gross evidence of calcification deposits at 10 weeks, and only 1 in 12 valves at 20 weeks. Minimal to mild calcific deposits were observed in one valve model 9300TFX, possibly as a result of an individual animal response The gross examination for the target organs (kidneys, liver, spleen, lung) at 10 and 20 weeks were all within normal limits, excluding one animal for the model 2800TFX at 20 weeks.
Clinical History and Hematology	All six 10-week and thirteen of the fourteen 20-week sheep were clinically normal prior to explants. One animal experienced an increased respiratory rate and effort two weeks post operative and remained on diuretic therapy until sacrifice. Clinical chemistry and complete blood count results were within normal limits for the majority of animals at implant and explant. Five animals, from test and control groups, showed moderately low platelet count. Among the remaining animals, some values were either slightly above or below the reported normal range but none was considered to clinically significant. Findings were comparable between all groups. None of the pre-implant and pre-explant abnormal hematology findings were considered to be clinically significant to affect the outcome of the study.
Hemodynamic Performance	In general, peak gradients and cardiac outputs at explants tended to be higher than at implant. The 9300TFX and 9000TFX valves had evidence of valvular insufficiency by contrast angiography. The gaps were located between the annuloplasty ring and the aortic wall and were a failure of the model and not a problem with the valve delivery or performance. One 2800TFX control valve had paravalvular gap from possible suture tear. Angiography evaluation at 20 weeks indicated that 5 of 6 test valves had grade 1-2 regurgitation and 1 of 6 had grade 3-4 regurgitation. For the 9000TFX control valve at 20 weeks, 4 of 6 had grade 1-2 regurgitation and 2 of 6 had grade 3-4 regurgitation. For the 2800TFX control valve at 20 weeks, 1 of 2 had grade 3-4 regurgitation and 1 of 2 had no evidence of regurgitation.
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.

Evaluation Parameter	Summary of Results
Gross Observations	General healing results were comparable among the three valve models at 20 weeks. There were no thrombus, valvular mineralization and vegetative growths in 17 of 18 valves. There was no migration, leaflet damage, material wear, or structural failure in 17 of 18 valves. Minimal thrombus formation with unknown etiology was observed in the inflow aspect and minimal leaflet transparency observed on the outflow aspect of a model 9300TFX; attributable to compression lines caused by valve crimping. All valves showed no gross evidence of calcification deposits at 10 weeks, and only 1 in 12 valves at 20 weeks. Minimal to mild calcific deposits were observed in one valve model 9300TFX, possibly as a result of an individual animal response The gross examination for the target organs (kidneys, liver, spleen, lung) at 10 and 20 weeks were all within normal limits, excluding one animal for the model 2800TFX at 20 weeks.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The clinical data presented in this section to establish a reasonable assurance of safety and effectiveness of the SAPIEN XT THV came from the following sources:

- Cohort B of the PARTNER II trial (G090216): randomized, inoperable patients, transfemoral (TF) delivery, 23 and 26 mm THVs (cf. section X.1)
- NR5: single-arm registry, inoperable patients, transfemoral delivery, 29 mm THV (cf. section X.2)
- NR1, NR4, and NR6: single-arm registry, inoperable patients, alternate access (NR1: transapical (TA) delivery of size 23 and 26 mm; NR4: transaortic (TAo) delivery of size 23 and 26 mm; and NR6: transapical delivery of size 29 mm; cf. section X.3)
- Edwards SOURCE XT Registry : single-arm, high risk patients, 23, 26, and 29 mm THVs, all access sites (cf. section X.4)

X.1 SUMMARY OF THE RANDOMIZED CLINICAL TRIAL

A. Study Design

Cohort B of the PARTNER 2 trial was a prospective, randomized, controlled, multicenter, pivotal trial study comparing the SAPIEN XT THV with the first generation SAPIEN THV in non-surgical patients who were candidates for the transfemoral approach. Patients were randomized in a 1:1 ratio to either TAVR with the SAPIEN XT THV (test arm) or TAVR with the SAPIEN THV (control arm). The valve sizes used in the trial included only the 23 and 26 mm ones.

The sample size was set to 500 patients based on a non-inferiority ratio of 1.35 at a one-sided alpha of 0.025, with the assumptions of a 1:1 randomization ratio, 43.6% event rate in both trial arms, 80% power, and 10% attrition rate, and other trial contingencies.

The primary safety and effectiveness endpoint was a non-hierarchical composite of death (all cause), disabling (major) stroke, and rehospitalization for symptoms of aortic stenosis and/or complications of the valve procedure at one year (Day 365). Major stroke and rehospitalization were evaluated by the Clinical Event Committee (CEC). Events occurring on day 365 or earlier were included in the evaluation. Events occurring after day 365 were not included.

Pre-specified secondary endpoints included days alive and out of the hospital, NYHA functional class, the distance covered during a 6 minute walk test (6MWT), and valve performance (assessed by echocardiography).

The analysis was based on the ratio of proportions. Let r_T denote the true event proportion in the test arm, and r_C denote the true event proportion in the control arm. The hypotheses were:

$$H_0: \ r_T/r_C \ \geq \ 1 + D$$

$$H_A: r_T/r_C \ < \ 1 + D$$

where D was the non-inferiority margin, and was set at 0.35.

The primary analysis population is the intent-to-treat (ITT) population. The event proportions r_T and r_C were computed using the Kaplan-Meier algorithm. The standard errors s_T and s_C were computed using Greenwood's formula. A two-sided 95% confidence interval for the logarithm of the ratio under the null hypothesis was constructed and then transformed back to produce confidence limits for the ratio itself. The null hypothesis was rejected at alpha = 0.025 if the upper limit of the confidence interval was less than 1.35.

1. Inclusion and Exclusion Criteria

   Enrollment in Cohort B was limited to patients who met the following inclusion criteria:

   (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 and an initial aortic valve area (AVA) of ≤ 0.8 cm^2 or indexed EOA < 0.5 cm^2/m^2. Qualifying echo must be within 45 days of the date of the procedure.
   (2) Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater.
   (3) The heart team agrees (and verified in the case review process) that valve implantation will likely benefit the patient.
   (4) The study patient or the study patient's legal representative has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.

(5) The study patient agrees to comply with all required post-procedure follow-up visits including annual visits through 5 years and analysis close date visits, which will be conducted as a phone follow-up.
(6) The heart team agrees that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity is ≥ 50%. The surgeons' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in the patient. At least one of the cardiac surgeon assessors must have physically evaluated the patient. All Cohort B patients must be approved by the Patient Selection and Procedure Management Steering or Executive Committee (at least 2 member votes, one must be a cardiac surgeon).
(7) The heart team agrees the patient is likely to benefit from valve replacement.

Patients were <u>not</u> permitted to enroll in Cohort B if they met any of the following exclusion criteria:

(1) Evidence of an acute myocardial infarction ≤ 1 month (30 days) 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) Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified.
(3) Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
(4) Preexisting mechanical or bioprosthetic valve in any position.
(5) Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease) Implantation of a permanent pacemaker is not excluded.
(6) Any patient with a balloon valvuloplasty (BAV) within 30 days of the procedure (unless BAV is a bridge to procedure after a qualifying ECHO).
(7) Patients with planned concomitant surgical or transcatheter ablation for Atrial Fibrillation.
(8) Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), Thrombocytopenia (Plt < 50,000 cell/mL).
(9) Untreated clinically significant coronary artery disease requiring revascularization.
(10) Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of screening evaluation.
(11) Need for emergency surgery for any reason.
(12) Hypertrophic cardiomyopathy with or without obstruction (HOCM).

(13) Severe ventricular dysfunction with LVEF < 20%.
(14) Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
(15) Active upper GI bleeding within 3 months (90 days) prior to procedure.
(16) A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.
(17) Native aortic annulus size < 18 mm or > 25 mm as measured by echocardiogram.
(18) Clinically (by neurologist) or neuroimaging confirmed stroke or transient ischemic attack (TIA) within 6 months (180 days) of the procedure.
(19) Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at the time of screening.
(20) Estimated life expectancy < 24 months (730 days) due to carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease.
(21) Expectation that patient will not improve despite treatment of aortic stenosis.
(22) Significant aortic disease, including marked tortuosity (hyperacute bend), aortic arch atheroma [especially if thick (> 5 mm), protruding or ulcerated] or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta.
(23) Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe obstructive calcification, severe tortuosity or minimum average vessel size less than 7 mm.
(24) Currently participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.
(25) It is known that the patient is currently enrolled in the PARTNER I Trial or was withdrawn from the PARTNER I Trial prior to endpoint analysis.
(26) Active bacterial endocarditis within 6 months (180 days) of procedure

The study used the following: an independent Data Safety Monitoring Board (DSMB) that was instructed to notify Edwards Lifesciences of any safety or compliance issues; a CEC that was responsible for adjudicating endpoint related events reported during the trial per definitions established *a priori*; an ECG Core Lab for independent analysis of rhythm and occurrence of myocardial infarction; and an Echocardiographic Core Lab for independently analyzing all echocardiograms.

2. Follow-up Schedule

All patients were followed during the index hospitalization, at 30 days, 6 months, 1 year, and annually thereafter. The key time points and evaluations conducted at all time points in the study are shown in **Table 11**.

Table 11: Schedule of Events - Cohort B

	Screening	Baseline	During procedure	Post Procedure	Discharge	30 D Follow-Up (-7 days; +14 days)	6 M (+ 30 days) Follow-up	1 Yr Follow-Up (± 60 days)	Telephone Follow-up after analysis close date (+30 days)	Annual Follow-Up ≥5 Y (± 60 days)
Physical assessment and Patient interview										
Operability Risk Assessment	**X**									
Informed Consent	**X**									
Medical History	**X**									
Physical Exam	**X**				**X**	**X**	**X**	**X**		**X**
CCS Angina	**X**				**X**	**X**	**X**	**X**		**X**
NYHA Classification	**X**				**X**	**X**	**X**	**X**		**X**
Cardiac Medications		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Event Assessment		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
NIH Stroke Score Assessment		**X**[1]			**X**[1]	**X**[1]	**X**[1]	**X**[1]		**X**
Modified Rankin Scale		**X**[1,]			**X**[1,2]	**X**[1, 2]	**X**[1, 2]	**X**[1, 2]		**X**
Barthel Index		**X**[1, 2]			**X**[1,2]	**X**[1, 2]	**X**[1, 2]	**X**[1, 2]		
Risk Score Assessments: STS Risk Score Logistic EuroSCORE	 **X** **X**									
Six Minute Walk Test (6MWT)		**X**				**X**		**X**		
MMSE	**X**									
Frailty Index		**X**								
Lab Measurements										
CBC with Differential and Platelet Count		**X**		**X**	**X**	**X**		**X**		
PTT or PT/INR		**X**		**X**	**X**					
CK/CKMB and/or Troponins		**X**[3]		**X**[4]						
Metabolic Panel (Sodium, Potassium, Creatinine, BUN)		**X**		**X**	**X**			**X**		
Liver Panel (ALT, AST)		**X**								
Albumin		**X**				**X**		**x**		
BNP		**X**			**X**	**X**		**X**		**X**
Plasma Free Hemoglobin & Haptoglobin		**X**				**X**		**X**		
Non-Invasive Tests										
ECG		**X**		**X**	**X**	**X**		**X**		
Chest X-ray		**X**			**X**	**X**		**X**		**X**
Transthoracic Echocardiogram (TTE)	**X**				**X**	**X**		**X**		**X**
Fluoroscopic imaging implanted valve			**X**			**X**[5]		**X**[5]		**X**[5]
Invasive Tests										

	Screening	Baseline	During procedure	Post Procedure	Discharge	30 D Follow-Up (-7 days; +14 days)	6 M (± 30 days) Follow-up	1 Yr Follow-Up (± 60 days)	Telephone Follow-up after analysis close date (+30 days)	Annual Follow-Up ≥5 Y (± 60 days)
CT Thoracic/Abdomen with visualization of iliac and femoral arteries	**X**									
Cardiac Catheterization	**X**									
Supra-aortic angiogram or TEE			**X**							
Invasive Hemodynamics			**X**							
Quality of Life Questionnaire										
Cohort B KCCQ, EQ5D, SF12		**X**				**X**		**X**		**X**

[1] A neurologist or a neurology fellow will assess the Cohort A and all Registries patients at Baseline, Post Procedure and Discharge. If the neurologist or neurology fellow is not available at the time of patient's baseline or discharge visit, a certified team member may perform the tests. A neurologist or neurology fellow must perform the Post Procedure assessment.

[2]. Barthel Index for any patient with a previous stroke.

[3] Baseline CK/CKMB and/or Troponins are required < 72 hours before the procedure.

[4] Post Procedure CK/CKMB and/or Troponins are required at 3 different time intervals: 1) the first lab draw post procedure (within 8 hours of exiting the cath lab or operating room) 2) the second lab draw 6 – 8 hours after the first lab draw 3) the third lab draw 6 – 8 hours after the second lab draw.

[5] For patients with abnormal chest x-ray findings related to valve integrity and position and patients with Adverse Events related to worsening valve function.

B. Accountability of PMA Cohort

Patients were treated between April 27, 2011 and February 20, 2012. The database reflected data collected through July 23, 2013 and included 560 patients enrolled at 28 investigational sites in the U.S., as shown in **Table 12**. At the time of database lock, of 560 patients enrolled in the study, 420 were still alive and 392 have completed the 1-year post-operative visit within window.

Table 12: Patient Disposition at Follow-up (ITT Population)

	Intent-to-Treat (ITT)	As-Treated (AT)	Valve Implant (VI)
SAPIEN	276	271	263
SAPIEN XT	284	282	280
Total	560	553	543

ITT= Intent To Treat population comprises of all patients randomized into one of the two treatment groups.
AT= As Treated population comprises of ITT patients who has a record of entry into Cath Lab
VI= Valve Implant population comprises of AT patients who has valve implanted

C. Patient Demographics and Baseline Parameters

The demographics of the study population are typical for a TAVR study performed in the US. As summarized in **Table 13**, it can be seen that the two study arms were well matched.

Table 13: Demographic and Baseline Characteristics
(ITT Population)

Characteristic	SAPIEN XT (N= 284)	SAPIEN (N= 276)	P Value
Age – yr	84.0 ± 8.65	84.6 ± 8.61	0.4439
Male sex — no. (%)	141 (49.6%)	142 (51.4%)	0.6736
STS score†	10.3 ± 5.38	11.0 ± 5.71	0.1461
Logistic EuroSCORE‡	18.8 ± 14.61	21.0 ± 16.92	0.2994
NYHA class — no. (%):			
I/II	9 (3.2%)	11 (4.0%)	0.6539
III/IV	275 (96.8%)	265 (96.0%)	
Coronary artery disease — no. (%)	186 (65.5%)	186 (67.4%)	0.6552
Previous myocardial infarction — no. (%)	55 (19.4%)	58 (21.0%)	0.6740
Previous intervention — no. (%)			
CABG	76 (26.8%)	72 (26.1%)	0.9237
PCI	90 (31.7%)	100 (36.2%)	0.2843
Balloon aortic valvuloplasty	51 (18.0%)	55 (19.9%)	0.5902
Cerebral vascular disease — no. (%)	31 (10.9%)	35 (12.7%)	0.6004
Peripheral vascular disease — no.. (%)	88 (31.0%)	75 (27.2%)	0.3524
COPD — no. (%):			
Any	84 (29.6%)	72 (26.1%)	0.3963
Oxygen-dependent	38 (13.4%)	43 (15.6%)	0.4734
Creatinine > 2 mg/dL (177 µmol/liter) — no. (%)	31 (10.9%)	33 (12.0%)	0.7907
Atrial fibrillation — no. (%)	104 (36.6%)	112 (40.6%)	0.3411
Permanent pacemaker — no. (%)	59 (20.8%)	47 (17.0%)	0.2814
Pulmonary hypertension — no. (%)	72 (25.4%)	57 (20.7%)	0.1934
Frailty§ — no. (%)	168 (59.2%)	166 (60.1%)	0.8633
Extensively calcified aorta — no. (%)	19 (6.7%)	11 (4.0%)	0.1896
Chest-wall deformity — no. (%)	10 (3.5%)	10 (3.6%)	>0.9999
Liver disease — no. (%)	12 (4.2%)	13 (4.7%)	0.8396
Echocardiographic findings			
Aortic-valve area — cm^2	0.6 ± 0.18	0.6 ± 0.17	0.7702
Mean aortic-valve gradient — mmHg	45.1 ± 13.64	45.2 ± 14.28	0.9655
Mean LVEF — %	52.3 ± 13.49	52.8 ± 13.80	0.7558
Moderate or severe mitral regurgitation** — no./total no. (%)	71/265 (26.8%)	79/255 (31.0%)	0.3330

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. ITT denotes intent to treat population, CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve implantation.
† 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.
‡ The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), which measures patient risk at the time of cardiovascular surgery, is calculated with the use of a logistic-regression equation. Scores range from 0% to 100%, with higher scores indicating greater risk. A logistic EuroSCORE higher than 20% indicates very high surgical risk.
§ Frailty was determined by the surgeons according to prespecified criteria.
** Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the AT cohort of 553 patients. The key safety outcomes for this study are presented below in **Tables 14** and **15**.

One unanticipated adverse device effects (UADEs) has been reported to date for the entire PARTNER II trial. The site's IRB determined valve migration into the left ventricle was not mentioned in the consent, and the consent was revised accordingly. However, both the Principal Investigator and Sponsor classified this event as "anticipated" based on the ICF, study protocol and IFU.

Four explants have been reported to date; three explants occurred at autopsy, and one SAPIEN XT valve was explanted on the day of the index procedure, which was complicated by aortic insufficiency and dissection of the aorta. CEC adjudicated endocarditis was reported for 3 patients (2 SAPIEN and one SAPIEN XT patient).

The composite adverse event rate involving CEC adjudicated major vascular complications and/or major stroke and/or minor stroke and/or TIA and/or acute stage 3 kidney injury to 30 days was not statistically different among trial arms at 30 days (p=0.3081), and neither were the individual components of this composite.

At 1 year, there was no significant difference between trial arms involving major stroke, minor stroke, life threatening/disabling bleeding, major bleeding, minor bleeding, acute kidney injury and permanent pacemaker.

CEC adjudicated serious adverse events are described in **Table 14** and **Table 15**.

Table 14: CEC Adjudicated Serious Adverse Events at 30-days and 1-Year (AT Population)*

Outcome [d]	30 Days		1-Year	
	SAPIEN XT (N=282)	SAPIEN (N=271)	SAPIEN XT (N=282)	SAPIEN (N= 271)
Death[b]				
From any cause	10/282 (3.5%)	12/271 (4.42%)	63/282 (22.34%)	61 / 271 (22.50%)
From cardiovascular cause	9/282 (3.2%)	10/271 (3.69%)	46/282 (16.31%)	46/271 (16.97%)
Major Stroke	9/282 (3.2%)	8/271 (2.95%)	13/282 (4.61%)	14/271 (5.17%)
Repeat hospitalization[c]	32/282 (11.3%)	28/271 (10.33%)	61/282 (21.63%)	61/271 (22.51%)
Death from any cause or major stroke or repeat hospitalization	48/282 (17.0%)	43/271 (15.87%)	105/282 (37.23%)	100/271 (36.90%)
Myocardial Infarction	5/282 (1.8%)	2/271 (0.74%)	19/282 (6.74%)	8/271 (2.95%)
Major Vascular Complications	32/282 (11.3%)	43/271 (15.87%)	35/282 (12.41%)	47/271 (17.34%)
Renal Failure[i]	10/282 (3.5%)	5/271 (1.85%)	16/282 (5.67%)	10/271 (3.69%)
Disabling Bleeding Event[e]	22/282 (7.8%)	34/271 (12.55%)	38/282 (13.48%)	52/271 (19.19%)
Cardiac Reintervention[f]	9/282 (3.2%)	13/271 (4.80%)	10/282 (3.55%)	13/271 (4.80%)

Endocarditis	0/282 (0.00%)	0/271 (0.00%)	1/282 (0.35%)	2/271 (0.74%)
New Atrial Fibrillation	6/186 (3.2%)	7/190 (3.68%)	10/154 (6.49%)	9/144 (6.25%)
New pacemaker	19/282 (6.7%)	16/271 (5.90%)	22/282 (7.80%)	21/271 (7.75%)

* AT= As Treated, NA= not applicable, TAVR = transcatheter aortic valve replacement. Data presented as n (%) of patients.
b. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
c. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
d. CEC adjudicated
e. Disabling bleeding: Fatal bleeding OR bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood of packed red blood cells (RBC) transfusion ≥4 units
f. Cardiac reintervention includes any intervention that repairs, alters or replaces a previously operated valve OR balloon aortic valvuloplasty OR Surgical aortic valve replacement OR valve in valve
i. Renal failure is defined as stage III acute kidney injury: Increase in serum creatinine to ≥300% (3 x increase compared with baseline) or serum creatinine of ≥ 4 mg/d (≥354 μmol/L) with an acute increase of at least 0.5 mg/dl (44 μmol/L)

Table 15: CEC Adjudicated Major Vascular Complications, Major Stroke, Minor Stroke, TIA and Acute Kidney Injury to 30 Days (AT Population)

	SAPIEN® (N=271)					**SAPIEN XT® (N=282)**					
VARC Event[1]	**Events**	**Patients with Event**	**No. Patients At Risk**	**KM Estimate [2]**	**Standard Error of KM**	**Events**	**Patients with Event**	**No. Patients At Risk**	**KM Estimate [2]**	**Standard Error of KM**	**p-value [3]**
Major Vascular Complications and/or Major Stroke and/or Minor Stroke and/or TIA and/or Acute Stage 3 Kidney Injury	71	56	209	0.207	0.025	59	49	228	0.174	0.023	0.3081
Major Vascular Complications	53	43	219	0.159	0.022	37	32	243	0.114	0.019	0.1180
Major Stroke	8	8	251	0.030	0.010	9	9	264	0.032	0.011	0.8738
Minor Stroke	3	3	253	0.011	0.006	3	3	269	0.011	0.006	0.9570
TIA	2	2	254	0.007	0.005	0	0	272	0.000	0.000	0.1475
Acute Stage 3 Kidney Injury	5	5	252	0.019	0.008	10	10	265	0.036	0.011	0.2218

Note: Events with missing or incomplete onset dates are excluded from the analysis.
[1] Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials consensus from the Valve Academic Research Consortium (VARC)
[2] Kaplan-Meier estimates are provided at day 30 and use the first event per patient. Note: Events occurring after Day 30 are not included in the analysis.
[3] p-values comparing SAPIEN XT (Test) vs. SAPIEN (Control) are computed using the log-rank test.

2. Effectiveness Results

The KM estimate for the primary endpoint was 0.377 in the SAPIEN arm and 0.372 in the SAPIEN XT arm, resulting in a relative risk ratio of 0.987 (95% CI 0.793, 1.228) and p=0.0024. Since the upper limit of the CI was < 1.35, non–inferiority was met (**Figure 10**). The same analyses were performed for the primary endpoint and the individual component of the composite events on the AT population, as demonstrated in **Figures 11-19** for the primary endpoint, all

cause mortality, all-cause mortality by STS score, landmark analysis of all cause mortality by STS score at 30-days (see discussion below), major stroke, and rehospitalization, respectively.

In the landmark analysis, the overall mortality at day 30 was reset to 0 for patients still at risk at day 30 and day 30 was relabeled as day 0 (i.e., re-zeroed). The Kaplan-Meier plots were produced based on the re-zeroed data, and all-cause mortality was analyzed to one year from the new day 0. Events that occurred before day 30 were not included in this analysis.

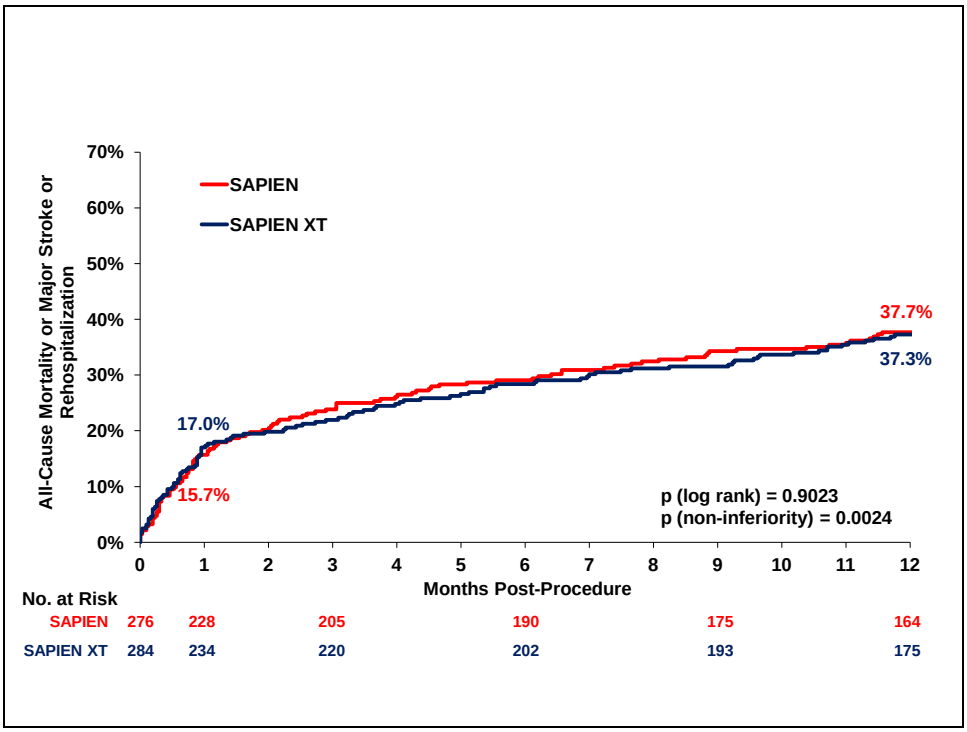

Figure 10: All-Cause Mortality and/or Major Stroke and/or Rehospitalization at 1 Year (ITT Population)

A tipping point analysis was conducted for the primary analysis to account for all possible combinations of missing data in the two trial arms. The non-inferiority was met, regardless of the imputation applied.

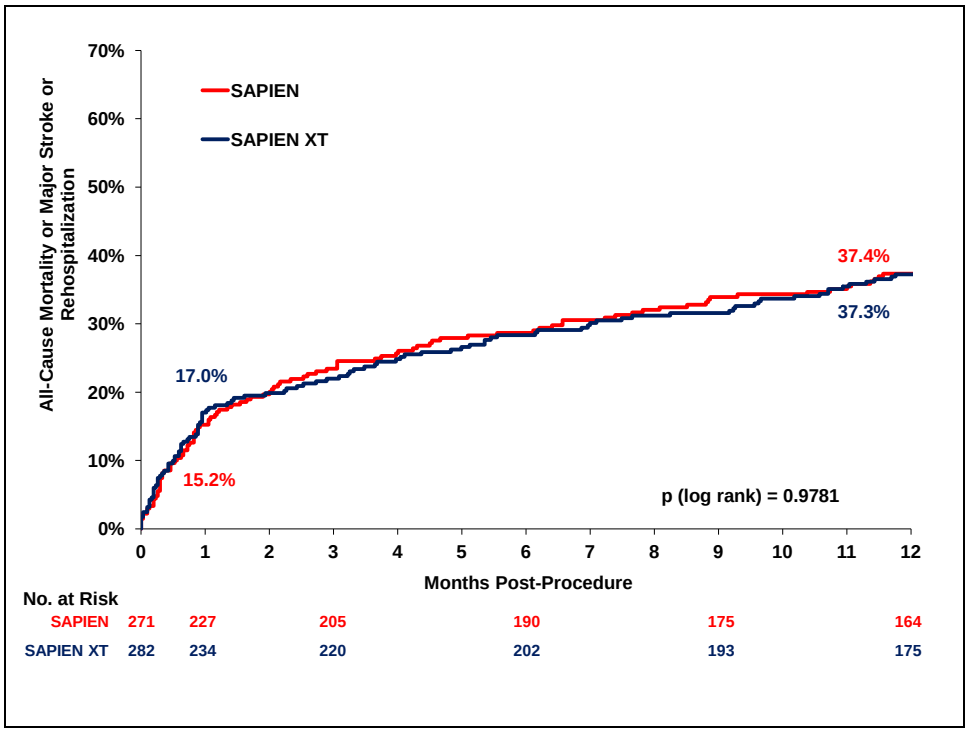

Figure 11: All-Cause Mortality or Major Stroke or Re-hospitalization at One Year (As-Treated Population)

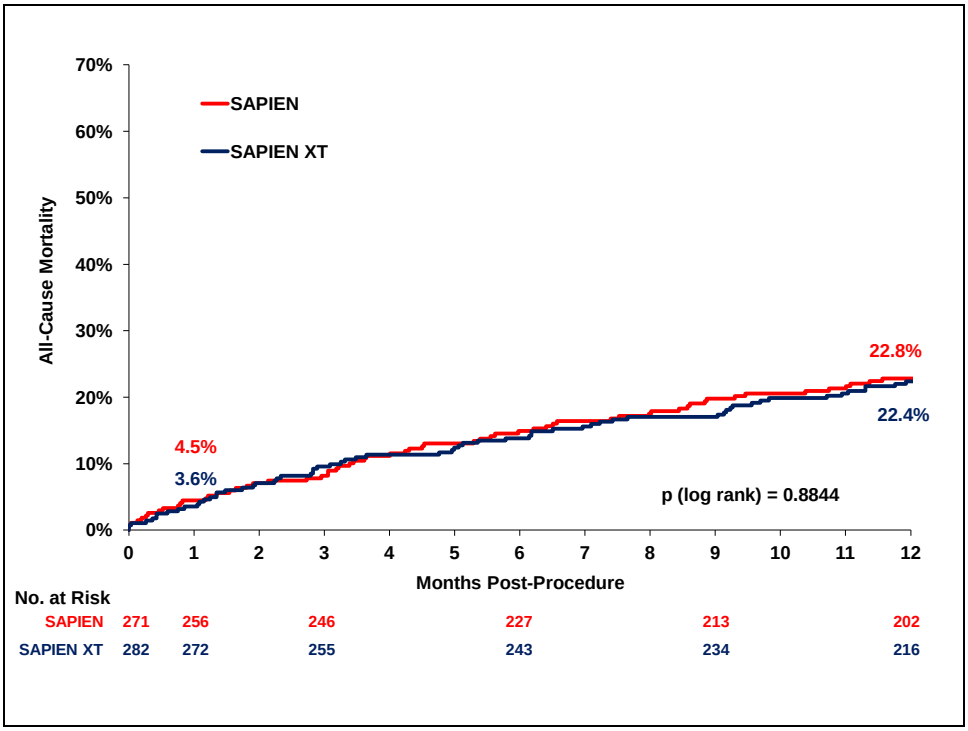

Figure 12: All-Cause Mortality at One Year (As-Treated Population)

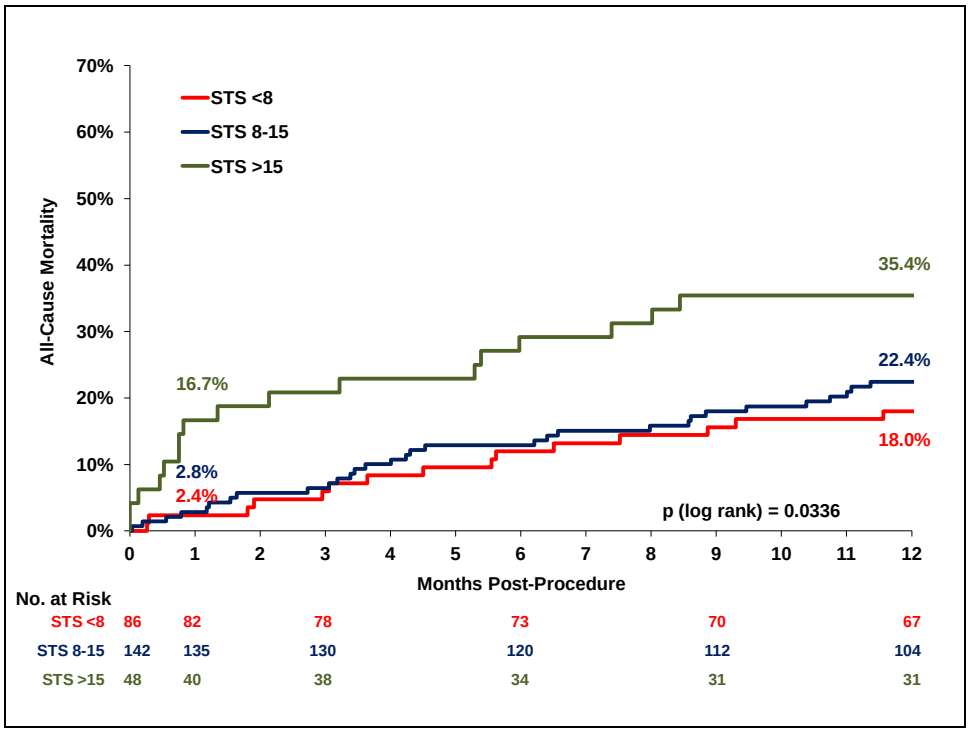

Figure 13: All-Cause Mortality by STS Score (SAPIEN), (Intent-to-Treat Population)

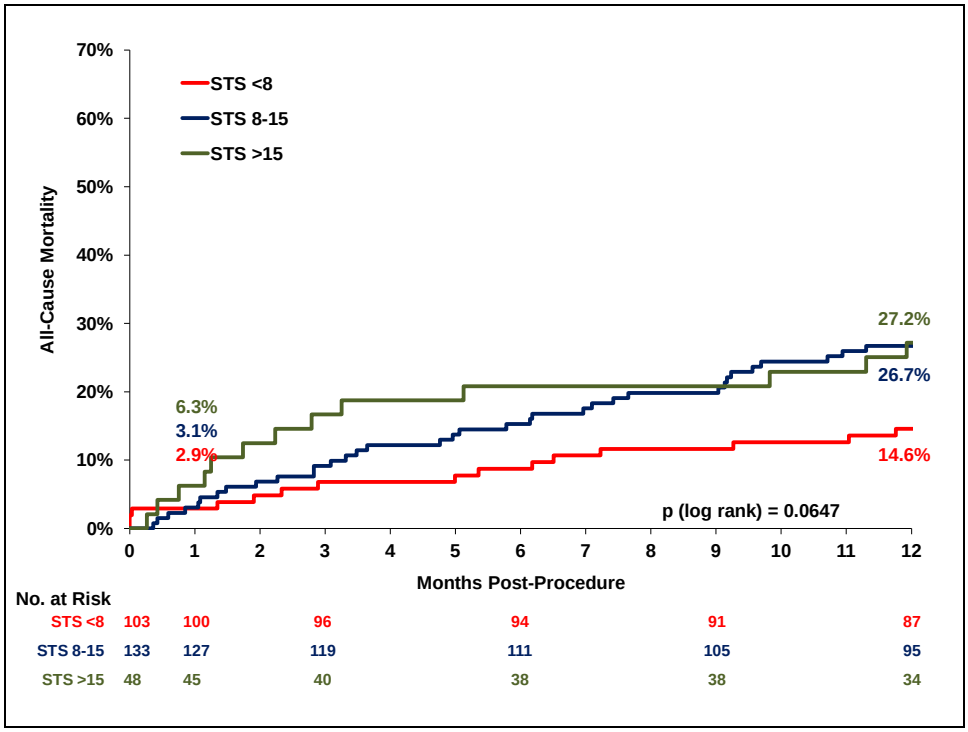

Figure 14: All-Cause Mortality by STS Score (SAPIEN XT), (Intent-to-Treat Population)

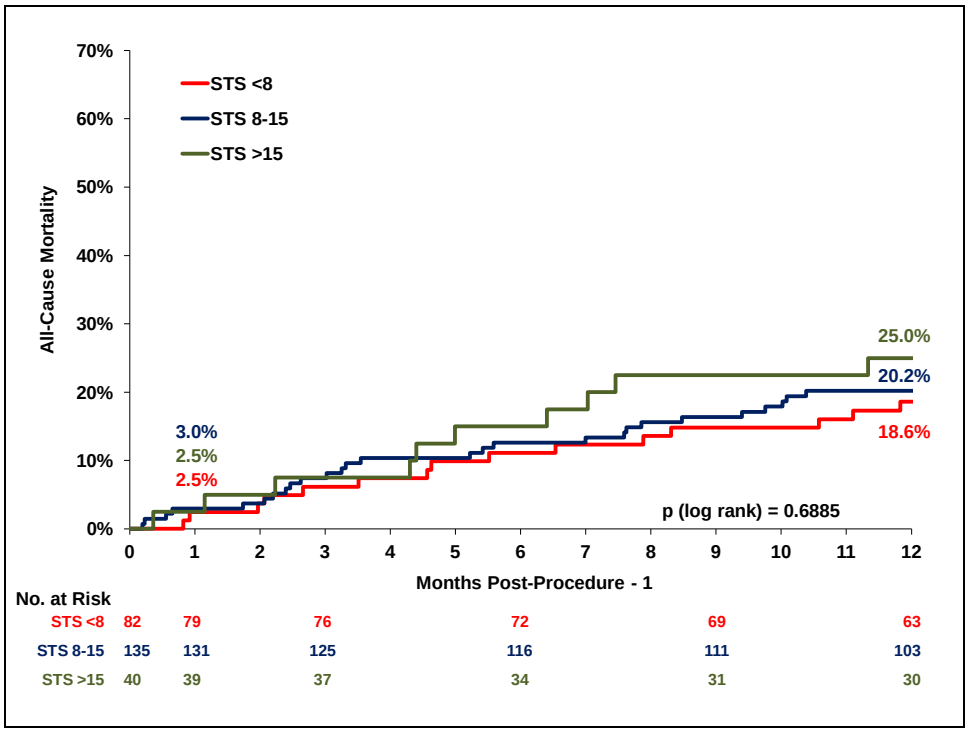

Figure 15: All-Cause Mortality by STS Score Re-Zeroing at 30 Days (SAPIEN), (Intent-to-Treat Population)

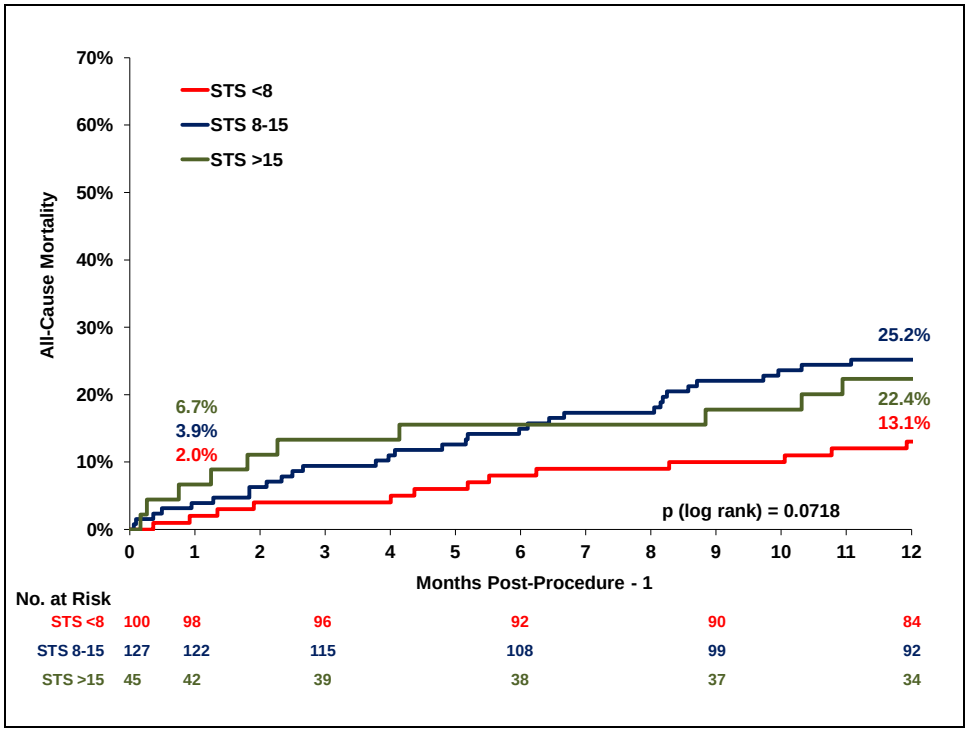

Figure 16: All-Cause Mortality by STS Score Re-Zeroing at 30 Days (SAPIEN XT), (Intent-to-Treat Population)

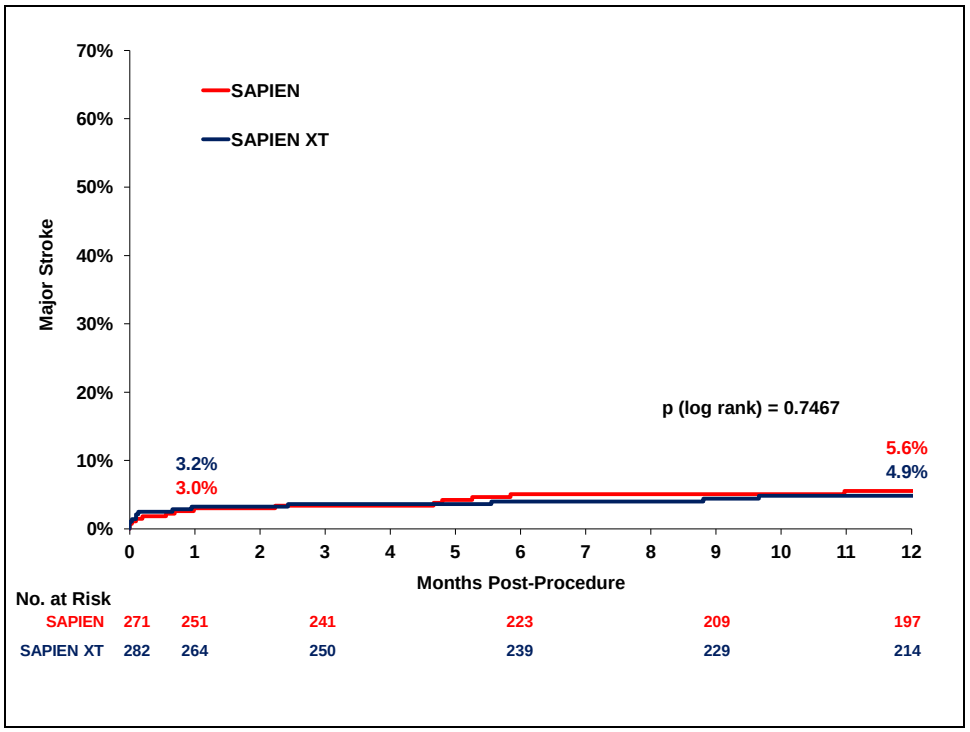

Figure 17: Major Stroke at One Year (As-Treated Population)

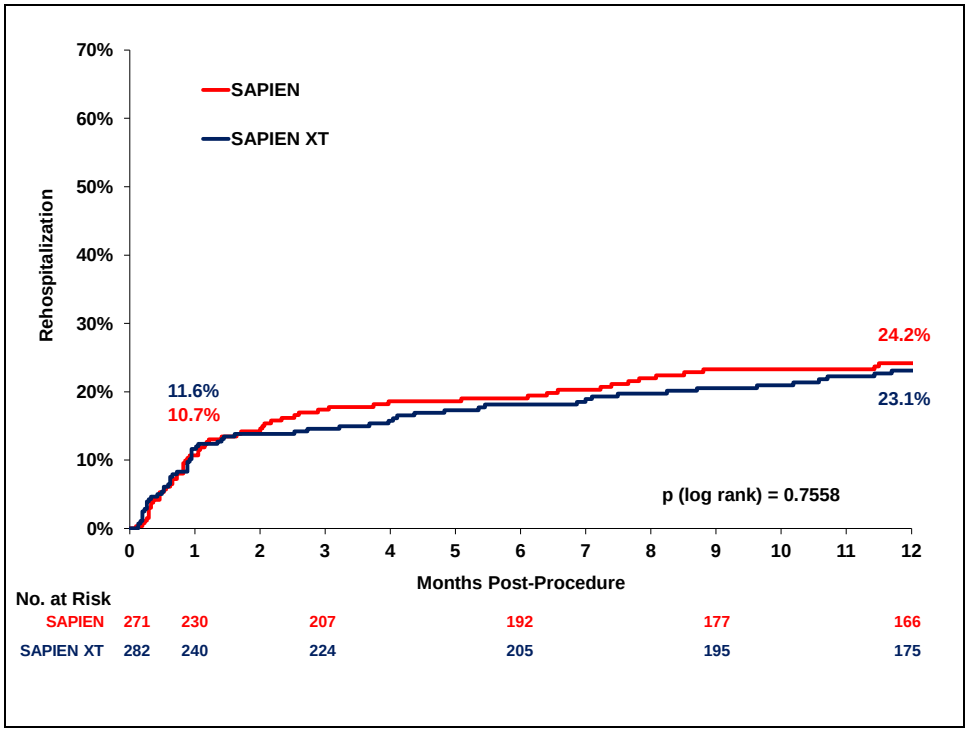

Figure 18: CEC Re-hospitalization at One Year (As-Treated Population)

Procedural parameters showed a significant reduction in catheter lab time duration (207.0 ± 57.8 min vs. 220.8 ± 70.2 min, p=0.0094) and total anesthesia time (197.6 ± 60.8 min vs. 212.0 ± 75.7 min, p=0.0196) in the SAPIEN XT arm. The SAPIEN XT arm also had a shorter total procedure time and lower incidence of multiple valve implants and aborted procedures.

a) Secondary Endpoints for Labeling that were Met

In the ITT population, the mean adjusted days alive and out of the hospital (DAOH) at 1 year was 299.2 ± 111.4 days for the SAPIEN group and 302.7 ± 108.7 days for the SAPIEN XT group. The difference between the two groups was 3.5 days (two sided 95% CI 1.8, 5.2) with p< 0.0001, indicating that non-inferiority was met.

In the SAPIEN group, the mean NYHA was 3.5 ± 0.6 at baseline and 1.8 ± 0.8 at 1 year, which constituted a reduction of 1.7 ± 0.9. In the SAPIEN XT group, the mean NYHA was 3.4 ± 0.6 at baseline and 1.7 ± 0.7 at 1 year, which constituted a reduction of 1.8 ± 0.9. The difference between the two groups was -0.13, (two sided 95% CI -0.32, 0.06) with p< 0.0001, indicating that non-inferiority was met. **Figure 19** illustrates the NYHA classification by visit for the ITT population.

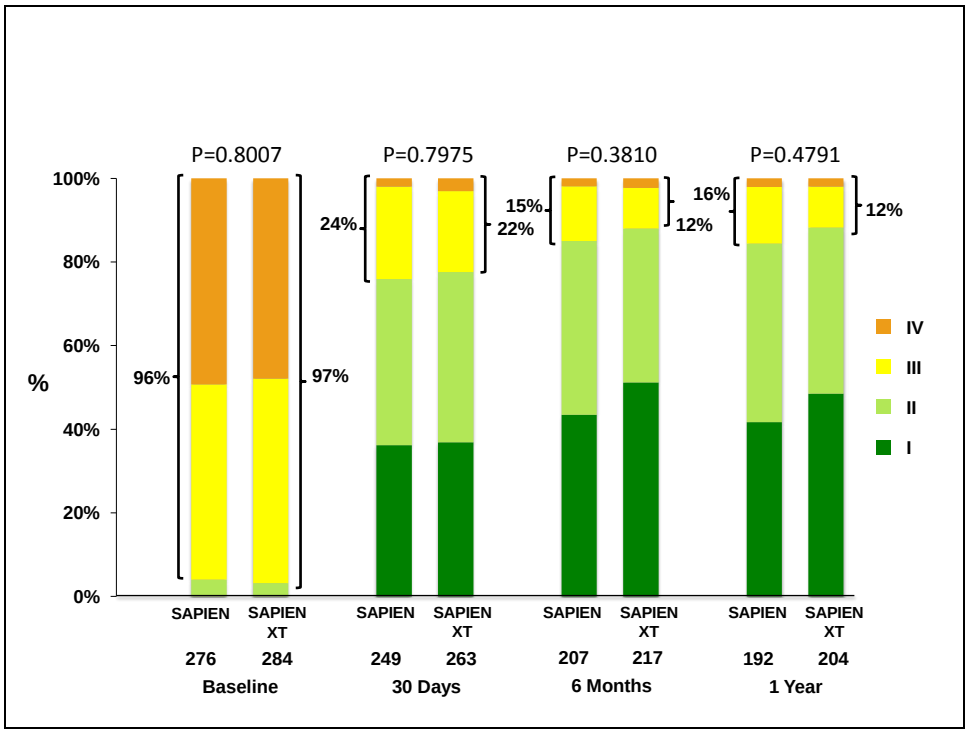

Figure 19: NYHA Class by Visit (ITT Population)

The hypothesis testing of the 6MWT at 1 year was based on a difference of 70 meters, which is considered clinically relevant. The mean 6MWT distance at 1 year was 132.3 ± 136.3 meters in the SAPIEN group, and 159.0 ± 138.5 meters in

the SAPIEN XT group. The difference between the two groups was 26.7 meters (95% CI 24.2, 29.2) with p<0.0001; therefore, non-inferiority was met.

The 6MWT improvement in the SAPIEN XT arm from baseline to 1 year was also compared. The improvement for each subject was computed, and the comparison was evaluated by a two-sided paired sample t-test. The mean improvement was 52.7 ± 111.5 meters, which was statistically significant (p<0.0001).

Another secondary endpoint for labeling was the EOA at 1 year. The hypothesis testing was based on a difference of 0.2 cm^2. In the SAPIEN group, the mean EOA was 0.6 ± 0.17 cm^2 at baseline and 1.5 ± 0.40 cm^2 at 1 year, which was an improvement of 0.9 ± 0.38 cm^2. In the SAPIEN XT group, the mean EOA was 0.6 ± 0.18 cm^2 at baseline and 1.5 ± 0.43 cm^2 at 1 year, a mean increase of 0.9 ± 0.41 cm^2. The difference between groups in change from baseline to 1 year was -0.01 (95% CI -0.15, 0.13; p=0.0038); therefore, non-inferiority was met.

Device success was defined as successful vascular access, delivery, and deployment and retrieval of delivery system; correct positioning; intended performance (aortic valve area > 1.2 cm^2 and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/s, without moderate or severe prosthetic valve AR); and only one valve implanted. The proportion of device success was 45.3% in the SAPIEN group and 58.5% in the SAPIEN XT group. The relative risk ratio of SAPIEN XT vs. SAPIEN was 0.759 (95% CI 0.582, 0.990; p<0.0001), indicating that non-inferiority was met.

b) Secondary Endpoints for Labeling that were not Met

Total aortic regurgitation was assessed by the core lab as 0 = None, 1+ = Trace, 2+ = Mild, 3+ = Moderate, and 4+ = Severe. Total regurgitation at one year was analyzed in the valve implant population. The change in mean total aortic regurgitation from baseline to 1 year was 0.1 ± 1.23 in the SAPIEN group, and 0.2 ± 1.38 in the SAPIEN XT group. The difference between groups in change from baseline to 1 year was 0.09 (95% CI -0.16, 0.34; p=0.1027); therefore, **non-inferiority was not met**.

c) Valve Performance

In the SAPIEN arm, the mean EOA increased from 0.6 ± 0.17 cm^2 at screening to 1.5 ± 0.43 cm^2 at discharge, and then maintained at 1.5 ± 0.38 cm^2 at 30 days and 1.5 ± 0.39 cm^2 at 1 year. In the SAPIEN XT arm, the mean EOA increased from 0.6 ± 0.18 cm^2 at screening to 1.6 ± 0.43 cm^2 at discharge, and then maintained at 1.6 ± 0.44 cm^2 at 30 days and 1.5 ± 0.43 cm^2 at 1 year (**Figure 20**).

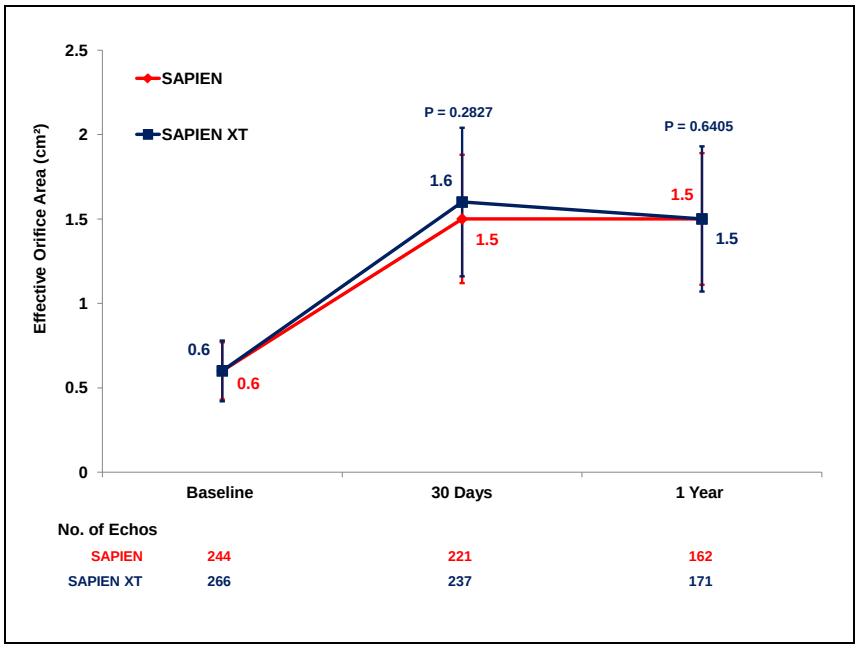

Figure 20: Effective Orifice Area (VI Population)

In the SAPIEN arm, the average mean gradient decreased from 45.2 ± 14.4 mmHg at screening to 12.1 ± 4.6 mmHg at discharge, and maintained at 10.4 ± 4.1 mmHg at 30 days and 11.0 ± 5.0 mmHg at 1 year. In the SAPIEN XT arm, the average mean gradient decreased from 45.2 ± 13.7 mmHg at screening to 10.3 ± 3.8 mmHg at discharge, and maintained at 10.0 ± 3.8 mmHg at 30 days and 11.4 ± 4.7 mmHg at 1 year (**Figure 21**).

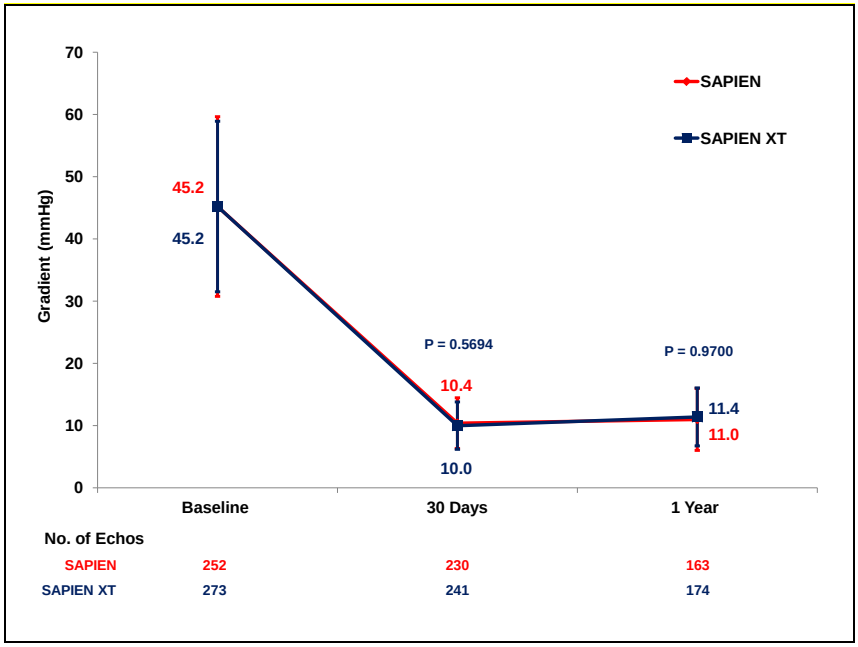

Figure 21: Mean Gradient (VI Population)

In the SAPIEN arm, the mean peak gradient decreased from 77.8 ± 23.0 mmHg at screening to 23.6 ± 8.8 mmHg at discharge, and maintained at 20.7 ± 7.9 mmHg at 30 days and 21.7 ± 9.4 mmHg at 1 year. In the SAPIEN XT arm, the mean peak gradient decreased from 78.8 ± 22.8 mmHg at screening to 20.5 ± 7.4 mmHg at discharge, and maintained at 19.8 ± 7.6 mmHg at 30 days and 22.8 ± 9.2 mmHg at 1 year (**Figure 22**).

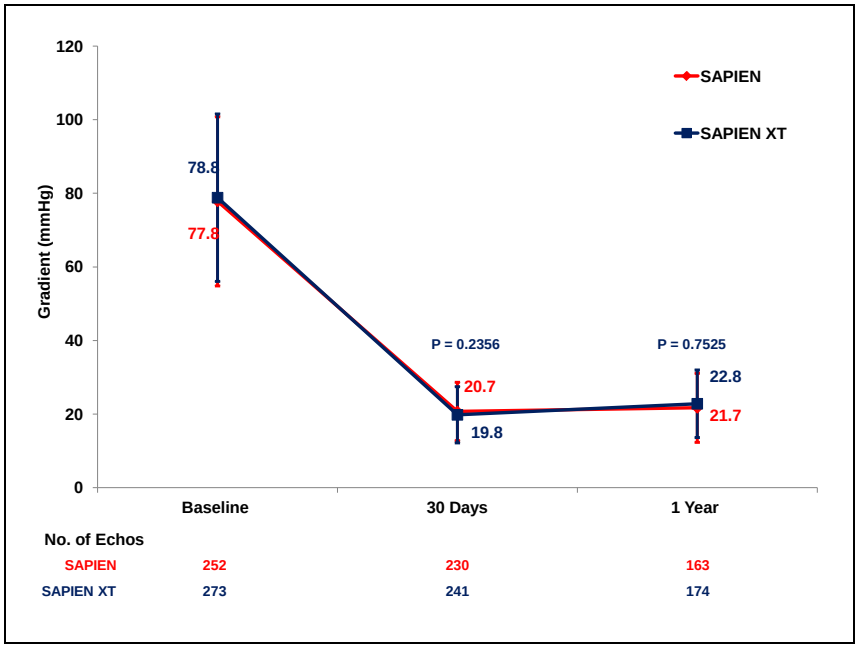

Figure 22: Mean Peak Gradient (VI Population)

In the SAPIEN arm, total aortic regurgitation was 1.7 ± 0.8 at baseline, and 1.8 ± 1.0 at 1 year. In the SAPIEN XT arm, total aortic regurgitation was 1.7 ± 0.9 at baseline, and 1.8 ± 1.0 at 1 year (**Figure 23**).

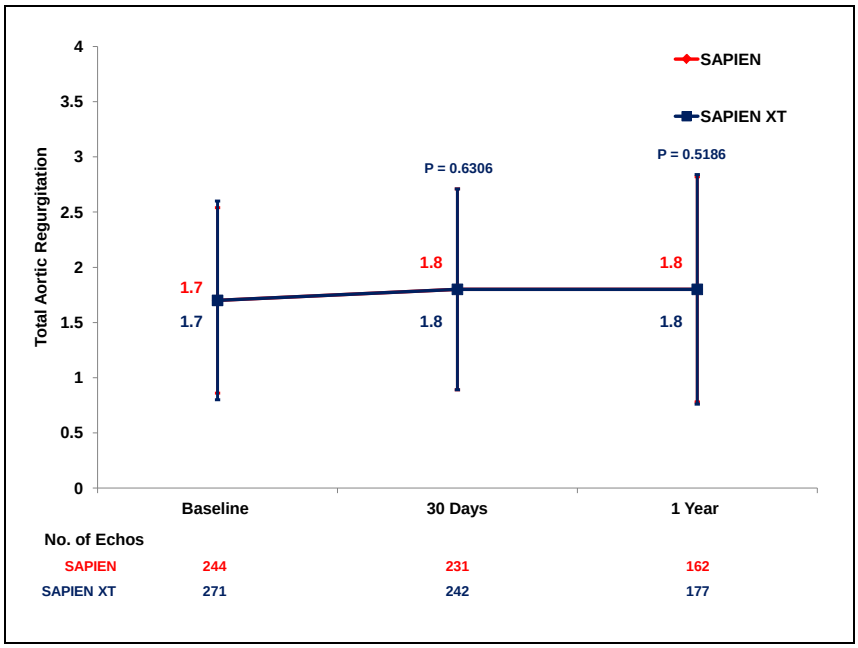

Figure 23: Total Aortic Regurgitation (VI Population)

d) Other

Quality of life at different time points as measured by the KCCQ clinical summary score is shown in **Figure 24**. The improvement over time was similar between the SAPIEN XT and SAPIEN groups.

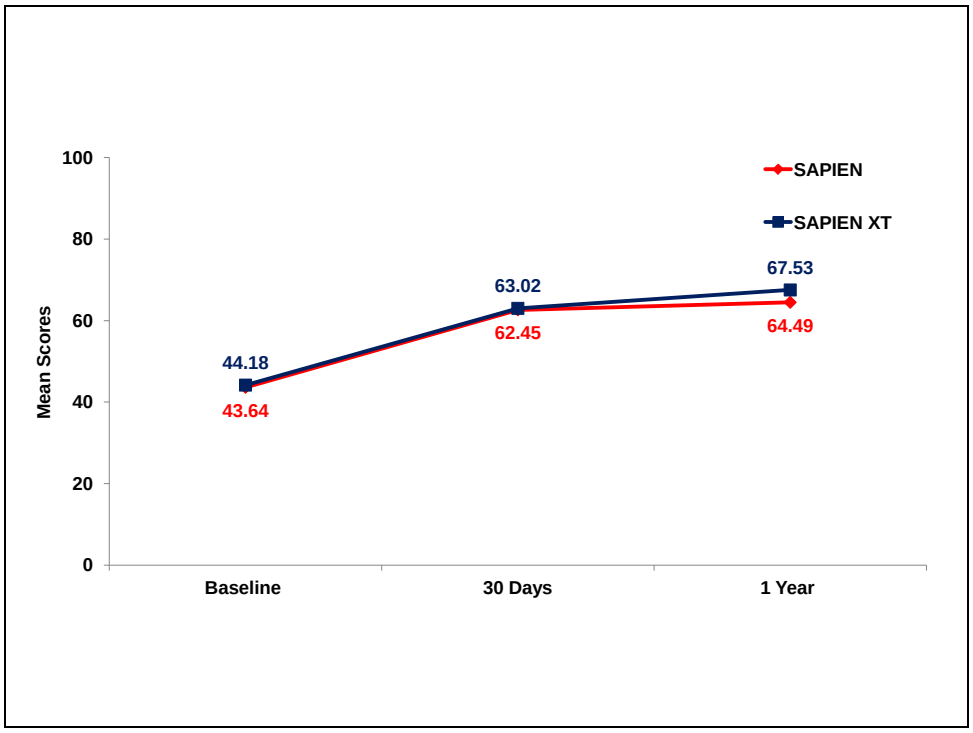

Figure 24: KCCQ Clinical Summary Score

3. Subgroup Analyses

Subgroup analyses of sex and preoperative atrial fibrillation were conducted for their potential association with outcomes. The non-inferiority primary endpoint was met in males as well as in patients with or without atrial fibrillation, but not met in females. However, the study was not powered to demonstrate non-inferiority in any subset of the study population.

E. **Financial Disclosure**

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conduction clinical studies covered by the regulation. The pivotal clinical study included 187 investigators of which none were full-time or part-time employees of the sponsor and nine had disclosable financial interests/ arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: 9 investigators
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

X.2 SUMMARY OF NESTED REGISTRY 5

A. Study Design

The 29 mm SAPIEN XT THV was not included in the randomized cohort of the trial because it was introduced later during the trial. A single arm, prospective observational nested registry, NR5, was designed to obtain data involving the 29 mm valve in inoperable, transfemoral access patients.

Patients were treated between October 12, 2012 and February 20, 2013. The database reflected data collected through July 22, 2013 and included 61 patients at 25 investigational sites.

1. Clinical Inclusion and Exclusion Criteria

   The inclusion and exclusion criteria for enrollment in NR5 were the same as those in Cohort B for the PARTNER II study, except that patients were required to have > 7mm femoral arteries and patients previously enrolled as a Cohort A control were not able to be enrolled in this registry.

2. Follow-up Schedule

   The follow-up schedule for the patients in NR5 was the same as that for Cohort B as described in Section X.1.A.2.

3. Clinical Endpoints

   The primary safety and effectiveness endpoint was freedom from all-cause mortality at 1-year. Pre-specified secondary endpoints included NYHA functional class, the distance covered during a 6-minute walk test (6MWT), and valve performance assessed by echocardiography. The results presented here are the 30-day data.

B. Accountability of the Nested Registry Patients

At the time of database lock, of 61 patients with treatment assigned in the nested registry, 56 patients completed the 30-day post-operative visit, as shown in **Table 16**.

Table 16: Patient Accountability for NR5

	Intent-to-Treat (ITT)	As-Treated (AT)	Valve Implant (VI)
NR5: 29mm SAPIEN XT TF	61	61	60

ITT= Intent To Treat population comprises of all patients received treatment assignment.
AT= As Treated population comprises of ITT patients who has a record of entry into Cath Lab
VI= Valve Implant population comprises of AT patients who has valve implanted

C. Patient Demographics and Baseline Parameters

The demographics of the study population are typical for a TAVR study performed in the US, as summarized in **Table 17**.

Table 17: Cohort B (Inoperable) Baseline Characteristics of the Patients and Echocardiographic Findings (ITT Population)

	NR5: SAPIEN XT TF
Characteristic	(N= 61)
Age - yr	83.3 ± 7.89
Male sex — no. (%)	61 (100.0%)
STS score†	8.3 ± 4.39
Logistic EuroSCORE‡	11.3 ± 13.75
NYHA class — no. (%):	
I/II	6 (9.8%)

III/IV	55 (90.2%)
Coronary artery disease — no. (%)	48 (78.7%)
Previous myocardial infarction — no./total no. (%)	14/61 (23.0%)
Previous intervention — no./total no. (%)	
CABG	34/61 (55.7%)
PCI	19/61 (31.1%)
Balloon aortic valvuloplasty	20/61 (32.8%)
Cerebral vascular disease — no./total no. (%)	10/61 (16.4%)
Peripheral vascular disease — no./total no.	16/61 (26.2%)
COPD — no. (%):	
Any	19 (31.1%)
Oxygen-dependent	6 (9.8%)
Creatinine > 2 mg/dL (177 μmol/liter) — no./total no. (%)	8/61 (13.1%)
Atrial fibrillation — no./total no.	30/61 (49.2%)
Permanent pacemaker — no./total no. (%)	18/61 (29.5%)
Pulmonary hypertension — no./total no. (%)	13/61 (21.3%)
Frailty§ — no./total no. (%)	30/61 (49.2%)
Extensively calcified aorta — no. (%)	3 (4.9%)
Chest-wall deformity — no. (%)	5 (8.2%)
Liver disease — no./total no. (%)	2/61 (3.3%)
Echocardiographic findings	
Aortic-valve area — cm^2	0.8 ± 0.16
Mean aortic-valve gradient — mmHg	40.3 ± 11.67
Mean LVEF — %	46.1 ± 14.52
Moderate or severe mitral regurgitation** — no./total no. (%)	15/56 (26.8%)

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. ITT denotes intent to treat population, CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve implantation.
† 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.
‡ The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), which measures patient risk at the time of cardiovascular surgery, is calculated with the use of a logistic-regression equation. Scores range from 0% to 100%, with higher scores indicating greater risk. A logistic EuroSCORE higher than 20% indicates very high surgical risk.
§ Frailty was determined by the surgeons according to prespecified criteria.
** Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

D. Safety and Effectiveness Results

The KM estimate at 30 days involving freedom from all-cause mortality was 94.9 ± 2.8% for NR5. **Figure 25** presents the number and percent of deaths to 30 days by procedure for the ITT population. In the NR5, all 3 expirations (4.9%) were cardiac related; 2 cardiac deaths were related to the procedure and one cardiac death was related to the device.

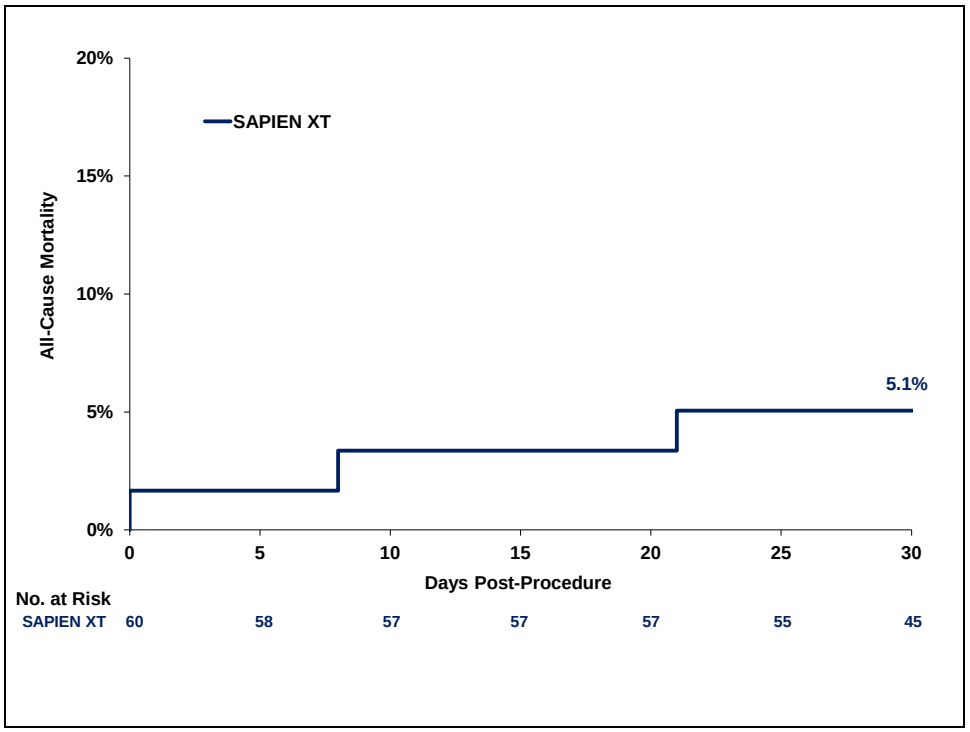

Figure 25: NR5 – All-Cause Mortality at 30 Days (Intent-to-Treat Population)

1. Safety Results

The analysis of safety was based on the AT cohort of 61 patients. The key safety outcomes for this study are presented below in **Tables 18** and **19**.

One explant has been reported to date; the explant occurred at autopsy. No cases of endocarditis were observed at 30 days. CEC adjudicated serious adverse events are described in **Table 18** and **Table 19**.

Table 18: NR5 – CEC Adjudicated Adverse Events to 30 days (AT Population)

Outcome [d]	Event Rate N=61
Death[b]	
From any cause	3/61 (4.9%)
From cardiovascular cause	3/61 (4.9%)
Major Stroke	0/61 (0.0%)
Myocardial Infarction	1/61 (1.6%)
Major Vascular Complications	5/61 (8.2%)
Renal Failure[i]	0/61 (0.0%)
Disabling Bleeding Event[e]	7/61 (11.5%)
Cardiac Reintervention[f]	0/61 (0.0%)
Endocarditis	0/61 (0.0%)
New Atrial Fibrillation	1/37 (2.7%)
New pacemaker	3/61 (4.9%)

* AT= As Treated, NA= not applicable, TAVR = transcatheter aortic valve replacement. Data presented as n (%) of patients.
b. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
c. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
d. CEC adjudicated
e. Disabling bleeding: Fatal bleeding OR bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood of packed red blood cells (RBC) transfusion ≥4 units
f. Cardiac reintervention includes any intervention that repairs, alters or replaces a previously operated valve OR balloon aortic valvuloplasty OR Surgical aortic valve replacement OR valve in valve
i. Renal failure is defined as stage III acute kidney injury: Increase in serum creatinine to ≥300% (3 x increase compared with baseline) or serum creatinine of ≥ 4 mg/d (≥354 µmol/L) with an acute increase of at least 0.5 mg/dl (44 µmol/L)

Table 19: Kaplan-Meier Event Rate for CEC Adjudicated Major Vascular Complications, Major Stroke, Minor Stroke, TIA and Acute Kidney Injury to 30 Days (AT Population)

	NR5: 29mm SAPIEN XT TF (N=61)				
VARC Event[1]	Events	Patients with Event	No. Patients At Risk	KM Estimate [2]	Standard Error of KM
Major Vascular Complications and/or Major Stroke and/or Minor Stroke and/or TIA and/or Acute Stage 3 Kidney Injury	5	5	39	0.083	0.036
Major Vascular Complications	5	5	39	0.083	0.036
Major Stroke	0	0	41	0.000	0.000
Minor Stroke	0	0	41	0.000	0.000
TIA	0	0	41	0.000	0.000
Acute Stage 3 Kidney Injury	0	0	41	0.000	0.000

Source: Table 3.5.1
Note: Events with missing or incomplete onset dates were excluded from the analysis.
[1] Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials consensus from the Valve Academic Research Consortium (VARC)
[2] Kaplan-Meier estimates are provided at Day 30 and used the first event per patient. Events occurring after Day 30 were not included in the analysis.

2. Effectiveness Results

For NR5, the mean change (negative value = improvement) in NYHA from baseline at 30 days was -1.6 ± 0.9. Device success was observed in 82.5%. The

mean hospitalization stay was 6.1 ± 6.3 days which included 2.4 ± 3.4 days in the ICU.

For NR5, mean EOA was 0.8 ± 0.16 cm^2 at baseline and 2.2 ± 0.53 cm^2 at 30 days (**Figure 26**), and the average mean gradient decreased from 40.3 ± 11.8 mmHg at baseline to 7.7 ± 2.8 mmHg at 30 days (**Figure 27**). The mean peak gradient decreased from 71.7 ± 20.8 mmHg at baseline to 15.5 ± 5.7 mmHg at 30 days (**Figure 28**).

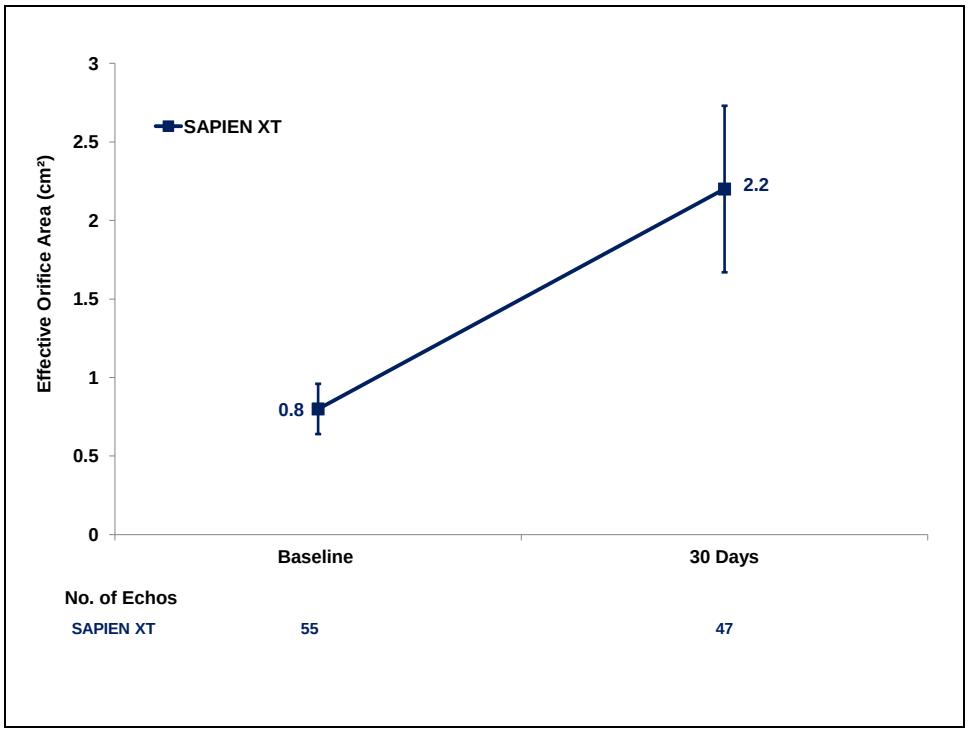

Figure 26: NR5 – Mean Effective Orifice Area - Baseline to 30 Days (Valve Implant Population)

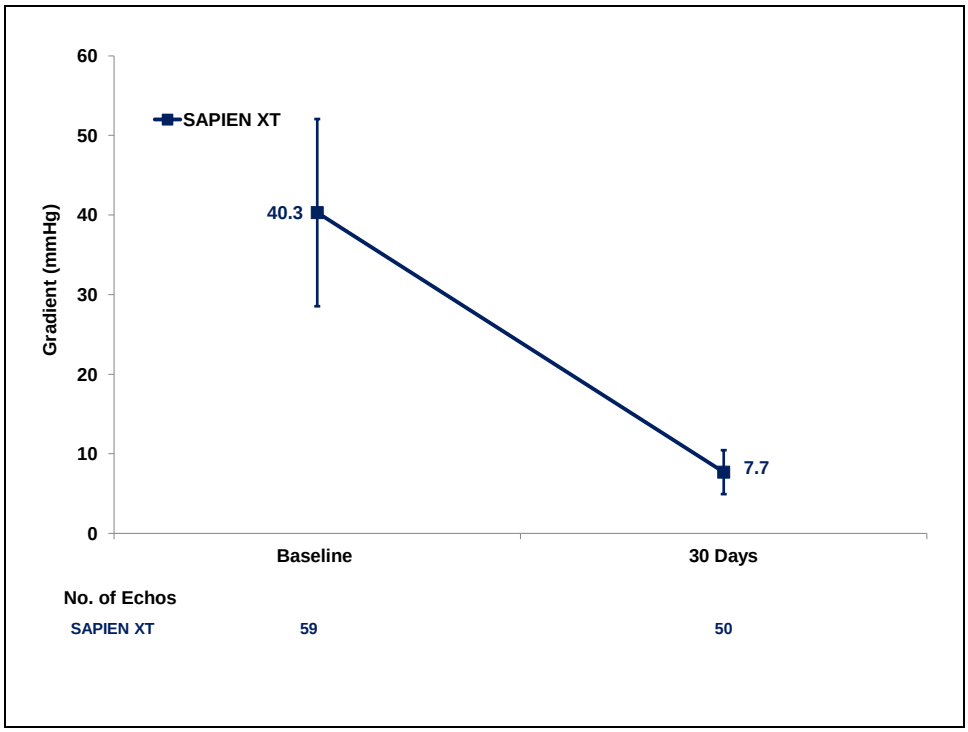

Figure 27: NR5– Mean Gradient – Baseline to 30 Days (Valve Implant Population)

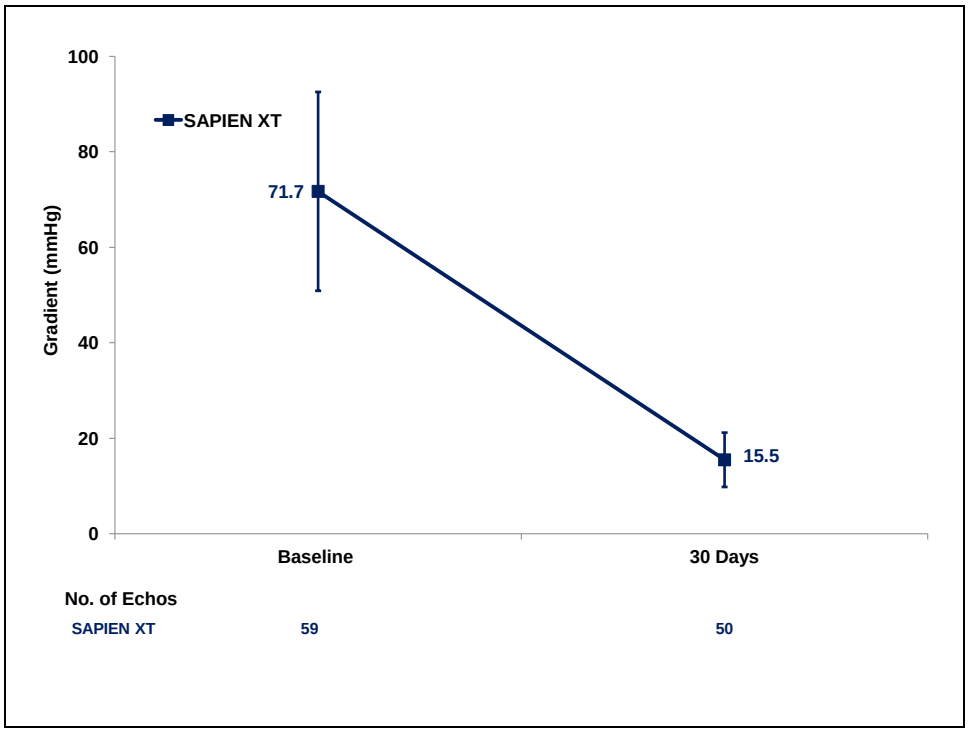

Figure 28: NR5– Mean Peak Gradient –Baseline to 30 days (Valve Implant Population)

Figure 29 illustrates the paravalvular aortic regurgitation at 30 days. No severe paravalvular aortic regurgitation was observed.

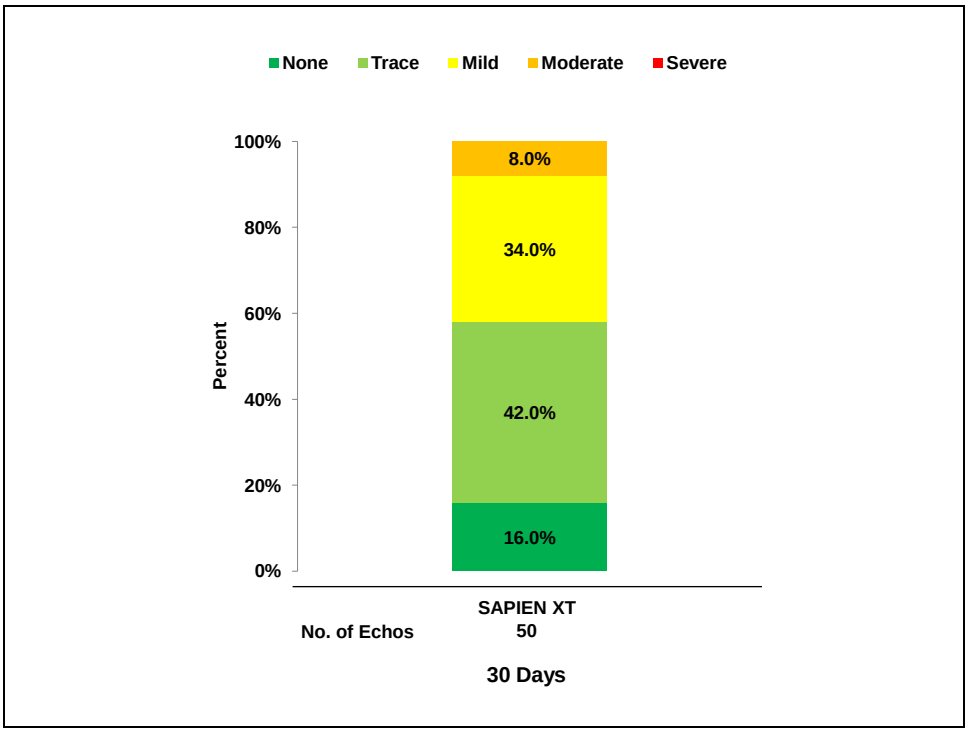

Figure 29: NR5 – Paravalvular Aortic Regurgitation by Grade at 30 Days (Valve Implant Population)

X.3 SUMMARY OF NESTED REGISTRIES 1, 4, AND 6

A. Study Design

Three single arm, prospective observational nested registries (NR) were designed to obtain data involving the Edwards SAPIEN XT THV in inoperable patients, as shown below:

- NR1 – Transapical delivery (sizes 23 and 26 mm)
- NR4 – Transaortic delivery (sizes 23 and 26 mm)
- NR6 – Transapical delivery (size 29 mm)

Patients were treated between March 6, 2012 and March 14, 2013. The database for the nested registries reflected data collected through February 06, 2014 and included 265 patients at 36 investigational sites.

1. Clinical Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for enrollment in NR1, NR4 and NR 6 were the same as Cohort B of the PARTNER II study, except that patients previously

enrolled as a Cohort A control were not able to be enrolled in any of these registries.

2. Follow-up Schedule

   The follow-up schedule for the patients in NR1, NR4 and NR6 was the same as that for Cohort B as described in Section X.1.A.2.

3. Clinical Endpoints

   The primary endpoint is freedom from mortality at one year. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and B. The results reported here are from the 30-day data.

B. Accountability of the Nested Registry Patients

At the time of database lock, of 279 patients with treatment assigned in the nested registries, 265 (95%) patients were treated and were available for analysis at the completion of the 30-day post-implant visit, as shown in **Table 20**.

Table 20: Patient Accountability for NR1, 4 and 6

	Intent-to-Treat (ITT)	As-Treated (AT)	Valve Implant (VI)
NR1, NR4, NR6: SAPIEN XT TA/TAo	279	265	263

C. Patient Demographics and Baseline Parameters

The demographics of the study population are typical for a TAVR study performed in the US, as described in **Table 21**.

Table 21: Cohort B (Inoperable) Baseline Characteristics and Echocardiographic Findings for NR1, NR4 and NR6 (AT Population)*

	SAPIEN XT (TA/TAo)
Characteristic	(N=265)
Age - yr	82.0 ± 7.79
Male sex — no. (%)	141/265 (53.2%)
STS score†	10.3 ± 5.51
Logistic EuroSCORE‡	13.2 ± 11.96
NYHA class — no. (%):	
I/II	24/264 (9.1%)
III/IV	240/264 (90.9%)
Coronary artery disease — no./total no. (%)	194/265 (73.2%)
Previous myocardial infarction — no./total no. (%)	56/265 (21.1%)
Previous intervention — no./total no. (%)	
CABG	118/265 (44.5%)
PCI	107/265 (40.4%)
Balloon aortic valvuloplasty	72/265 (27.2%)
Peripheral vascular disease — no./total no. (%)	150/265 (56.6%)
COPD — no./total no. (%):	
Any	101/265 (38.1%)
Oxygen-dependent	41/265 (15.5%)
Creatinine > 2 mg/dL (177 μmol/liter) — no./total no. (%)	28/265 (10.6%)
Atrial fibrillation — no./total no. (%)	95/265 (35.8%)
Permanent pacemaker — no./total no. (%)	43/265 (16.2%)
Pulmonary hypertension — no./total no. (%)	34/254 (13.4%)
Frailty§ — no./total no. (%)	97/254 (38.2%)
Extensively calcified aorta — no./total no. (%)	42/254 (16.5%)
Chest-wall deformity — no./total no. (%)	6/254 (2.4%)
Liver disease — no./total no. (%)	9/265 (3.4%)
Echocardiographic findings	
Aortic-valve area — cm^2	0.7 ± 0.19
Mean aortic-valve gradient — mmHg	41.2 ± 12.17
Mean LVEF — %	52.5 ± 13.37
Moderate or severe mitral regurgitation** — no./total no. (%)	70/232 (30.2%)

* Plus–minus values are mean ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. AT denotes As Treated population, CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve implantation.
† 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.
‡ The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), which measures patient risk at the time of cardiovascular surgery, is calculated with the use of a logistic-regression equation. Scores range from 0% to 100%, with higher scores indicating greater risk. A logistic EuroSCORE higher than 20% indicates very high surgical risk.
§ Frailty was determined by the surgeons according to prespecified criteria.
** Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

D. Safety and Effectiveness Results

The incidence of all cause mortality at 30 days was 8.0% (**Figure 30**). The incidence of all cause mortality or major stroke or re-hospitalization was 11.8% (**Figure 31**).

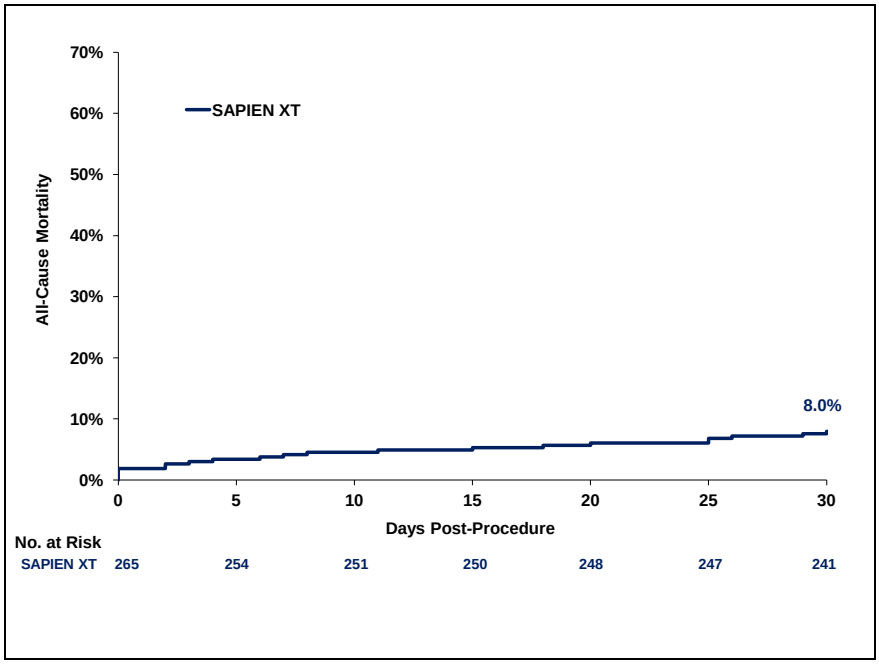

Figure 30: All-Cause Mortality at 30 days - TA/TAo As-Treated Population (NR1, NR4, NR6)

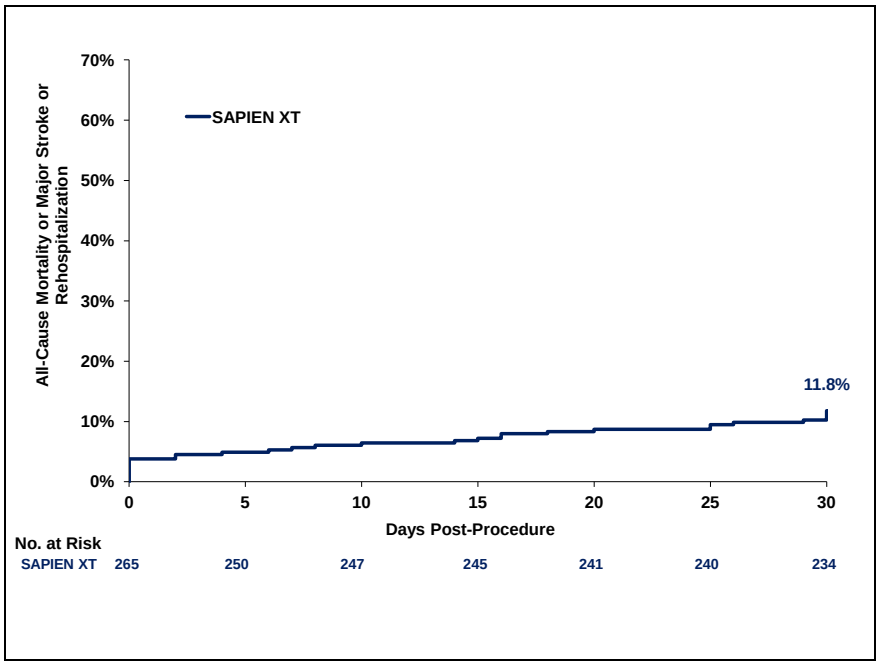

Figure 31: All-Cause Mortality or Major Stroke or Re-hospitalization at 30 days - TA/TAo As-Treated Population (NR1, NR4, NR6)

1. Safety Results

The safety results are summarized in **Tables 22** and **23**.

Table 22: Cohort B (Inoperable) Clinical Outcomes at 30 days for NR1, NR4 and NR6 (AT Population)*

Outcome[a]	SAPIEN XT (N=265)
Death from any cause	21/265 (7.9%)
Major Stroke	5/265 (1.9%)
Repeat hospitalization[b]	8/265 (3.0%)
Death from any cause or major stroke or repeat hospitalization	31/265 (11.7%)
Myocardial Infarction	4/265 (1.5%)
Major Vascular Complications	15/265 (5.7%)
Renal Failure[c]	7/265 (2.6%)
Disabling Bleeding Event[d]	30/265 (11.3%)
Cardiac Reintervention[e]	8/265 (3.0%)
Endocarditis	0/265 (0.0%)
New Atrial Fibrillation[f]	9/167 (5.4%)
New pacemaker	12/265 (4.5%)

* AT= As Treated, NA= not applicable, TAVR = transcatheter aortic valve replacement. Data presented as n (%) of patients.
a. CEC adjudicated
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Renal failure is defined as stage III acute kidney injury: Increase in serum creatinine to ≥300% (3 x increase compared with baseline) or serum creatinine of ≥ 4 mg/d (≥354 μmol/L) with an acute increase of at least 0.5 mg/dl (44 μmol/L)
d. Disabling bleeding: Fatal bleeding OR bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood of packed red blood cells (RBC) transfusion ≥4 units
e. Cardiac reintervention includes any intervention that repairs, alters or replaces a previously operated valve OR balloon aortic valvuloplasty OR Surgical aortic valve replacement OR valve in valve
f. Based on 163 patients at 30 days

Table 23: Conduction Disturbance Requiring Pacemaker to 30 Days for NR1, NR4 and NR6 (CEC Adjudicated) – AT Population

	SAPIEN XT (TA/TAo) (N=265)	
Event	Events	Patients with Event
New Permanent Pacemaker- All Patients[1]		
0-30 Days	12	12/265 (4.5%)
New Permanent Pacemaker – Patients without pre-procedural pacemaker[2]		
0-30 Days	12	12/222 (5.4%)

[1] Subjects with pacemaker or ICD at baseline are included (all patients included in denominator).
[2] Subjects with pacemaker or ICD at baseline are excluded (patients with baseline pacemaker/ICD subtracted from denominator).

2. Effectiveness Results

The mean EOA was 0.7 ± 0.19 cm^2 at baseline and 1.6 ± 0.43 cm^2 at 30 days, and the average mean gradient decreased from 41.2 ± 12.17 mmHg at baseline to 8.6 ± 3.59 mmHg at 30 days (**Figures 32** and **33**). The mean peak gradient decreased from 73.2 ± 21.51 mmHg at baseline to 17.7 ± 7.30 mmHg at 30 days.

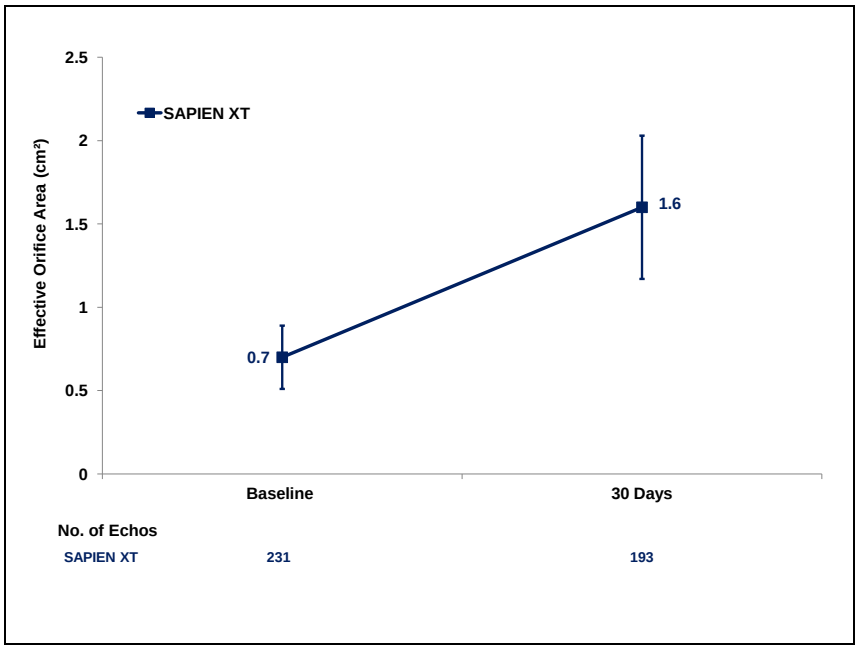

Figure 32: Echocardiographic Findings: Effective Orifice Area – TA/TAo Valve Implant Population (NR1, NR4, NR6)

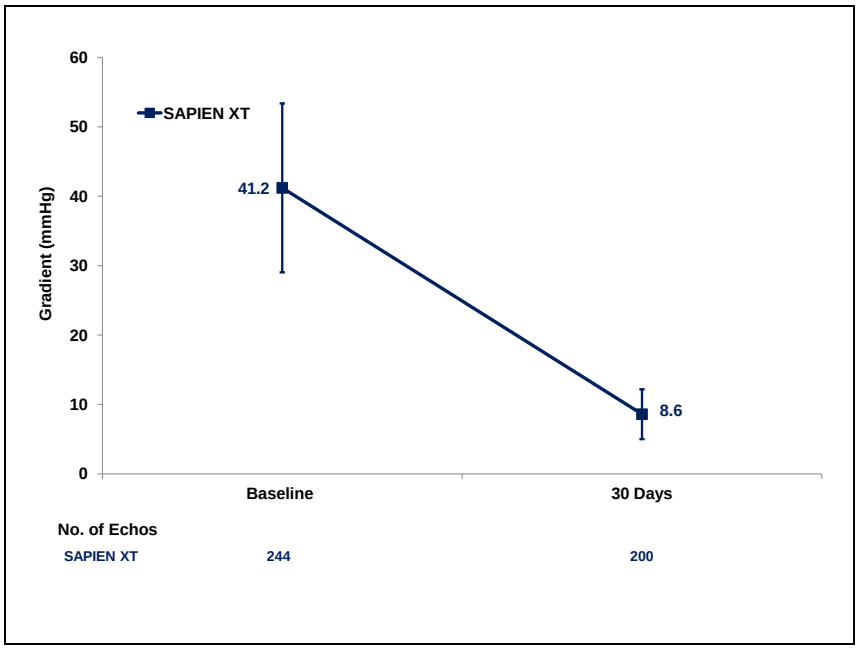

Figure 33: Echocardiographic Findings: Mean Gradient – TA/TAo Valve Implant Population (NR1, NR4, NR6)

NYHA decreased from 3.2 ± 0.61 at baseline to 1.9 ± 0.88 at 30 days. The mean change was -1.3 ± 1.10 (**Table 24** and **Figure 34)**. The mean KCCQ score increased by about 7 points at 30 days (**Figure 35**).

Table 24: NYHA Functional Class By Visit for NR1, NR4 and NR6 – AT Population

	SAPIEN XT (N=265)				
Visit	I	II	III	IV	Total
Baseline	1	23	158	82	264
30 Days	84	88	45	12	229

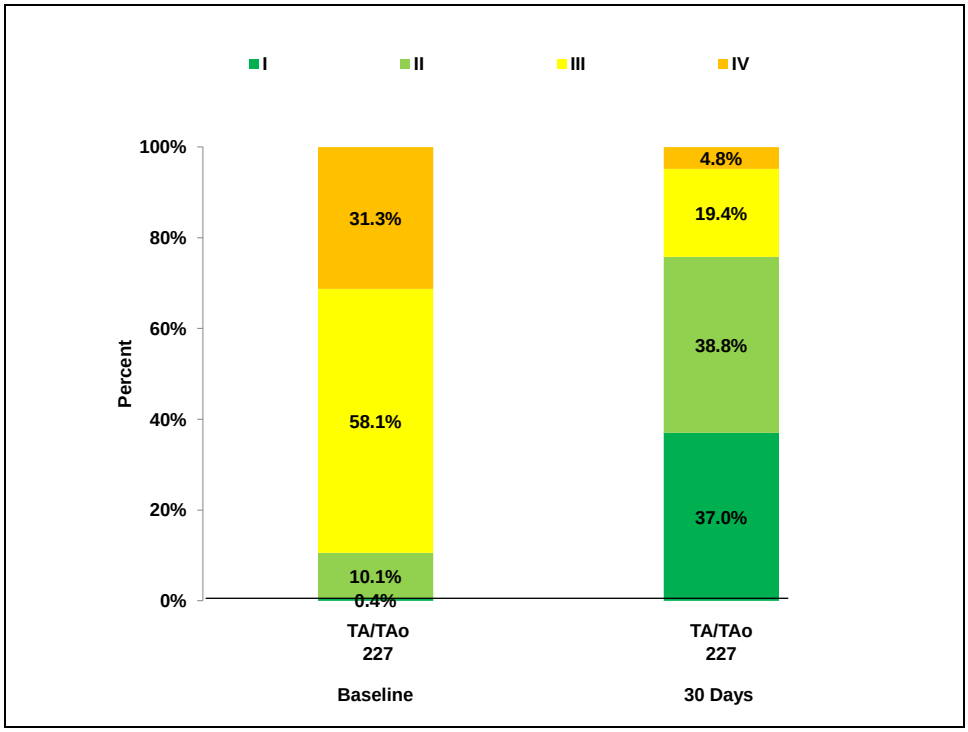

Figure 34: NYHA Class by Visit – TA/TAo Valve Intent-to-Treat Population (NR1, NR4, NR6)

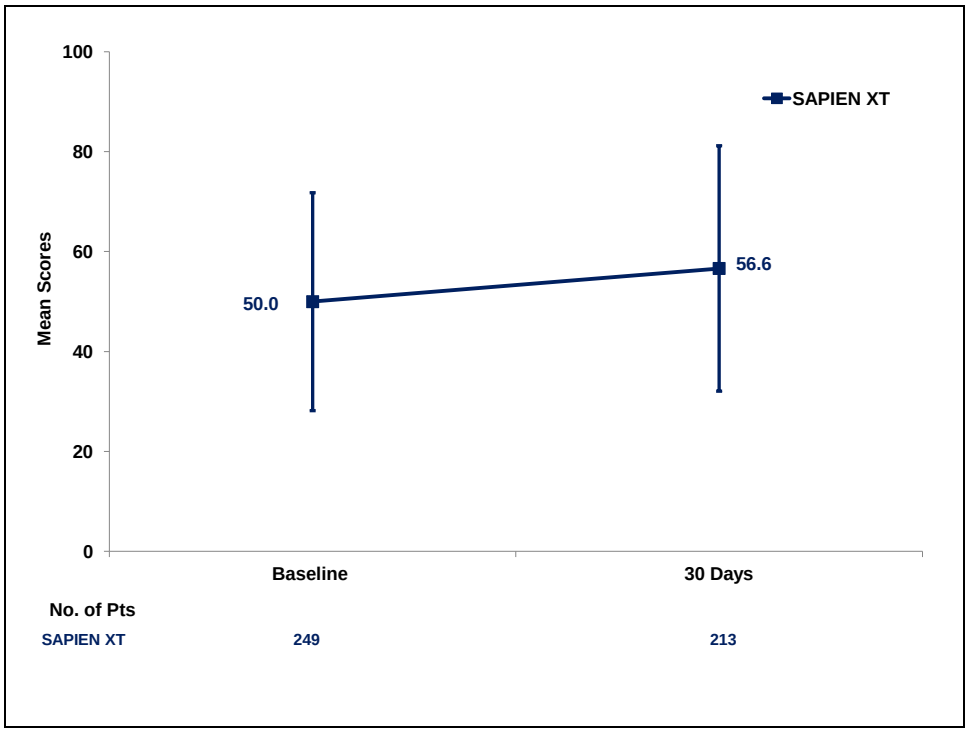

Figure 35: KCCQ Clinical Summary Score – TA/TAo As-Treated Population (NR1, NR4, NR6)

3. Conclusion
   The results of the nested registry support the use of the SAPIEN XT THV for the treatment of aortic stenosis in patients who are not suitable for transfemoral access.

X.4 SUMMARY OF SOURCE XT CLINICAL DATA

Note that the clinical results presented in sections X.1-X.3 were from the Cohort B of the PARTNER II trial, which included the inoperable patients. As per the protocol, the high risk patients are part of the Cohort A, which includes both intermediate and high risk patients (i.e., STS score ≥ 4) and is currently ongoing. After reviewing the data for the inoperable patient cohort, FDA proactively decided to expand the review of the PMA to include high risk patients as well. This decision was based on a significant public health need and existing scientific evidence, as detailed below:

(1) The SAPIEN device has been shown to be reasonably safe and effective for both inoperable and high risk patients (PARTNER IB & IA).
(2) SAPIEN XT has been demonstrated to be noninferior to SAPIEN in a head-to-head comparison in the inoperable patients (PARTNER IIB).
(3) As compared with the SAPIEN THV with the RetroFlex 3 delivery system, the SAPIEN XT THV with the NovaFlex+ delivery system has been demonstrated to improve procedural outcomes and reduce vascular complications.
(4) If SAPIEN XT is only approved for inoperable patients, high risk patients will not have on-label access to this new device iteration until the PARTNER IIA PMA is approved, despite all of the advantages that SAPIEN XT has over SAPIEN. This

creates an unforeseen challenging situation for both clinical practice and the public health need.

(5) There has been no indication so far that suggests a prosthetic heart valve will behave differently in hydrodynamic performance in patients of different risk strata. Although the benefit/risk profile of the same prosthetic heart valve might be different in patients of different risk strata, this is likely not the result of the valve performance, but the result of the underlying comorbidities of the patients. As such, it is reasonable to infer that SAPIEN XT will likely be noninferior to SAPIEN in the high risk patients.

Following the decision, FDA worked with the firm to identify available clinical data to support the high risk indication. In order to maintain the integrity of the Cohort A trial, data from that cohort were not included. The firm subsequently identified the SOURCE XT Registry data to be the most direct and relevant data set, which is summarized below.

A. Study Design

SOURCE XT was the first post-approval study conducted with the 23, 26, and 29 mm SAPIEN XT THVs following commercial availability of the device in the European Union. It was an international, multi-center, observational registry study of consecutive patients undergoing transcatheter aortic valve replacement (TAVR) with the SAPIEN XT THV. The purpose of the study was to expand on existing data sets, to identify patient characteristics and indicators related to complications and clinical benefits for patients with symptomatic severe calcific degenerative aortic stenosis who are undergoing treatment with the SAPIEN XT THV.

Patients were treated between July 20, 2010 and November 9, 2011. The database for SOURCE XT reflected data collected through June 21, 2013. Patient data were collected at discharge, 30 days, and 12 months post-implant, and annually thereafter for up to 5 years to observe trends in patient characteristics and outcomes over time.

B. Safety and Effectiveness Results

A total of 2688 patients were enrolled. The vast majority of patients (96%) were treated with either the transfemoral (TF; 62.7%) or transapical (TA; 33.3%) approach. Only a small proportion of patients were treated with transaortic (TAo; 3.76%) or subclavian (0.29%) approach. The data for the 29 mm valve were for TA and TAo delivery only. The results summarized in this section only include the TF, TA and TAo approaches (n=2680).

The KM event rates at 30 days post implant for the TF, TA/TAo population were 6.2% for all-cause death, 3% for cardiac death, 3.6% for stroke, 6.6% for major vascular complication, 14.9% for major/life threatening bleeding, 10.2% for major bleeding, 17.8% for renal failure or AKI, and 9.5% for new permanent pacemakers. The corresponding event rates at 1 year were 19.5% for all-cause

death, 9.5% for cardiac death, 6.3% for stroke, 17.3% for major/life-threatening bleeding, 12% for major bleeding, 7.2% for major vascular complications, 20.5% for renal failure or AKI, and 11% for new permanent pacemakers.

Demographic and baseline characteristics are described in **Table 25**. The key safety outcomes for this study are presented below in **Table 26.**

Table 25: SOURCE XT (High Risk) Baseline Characteristics of the Patients and Echocardiographic Findings (AT Population)

	Transfemoral	**TA/TAo Pooled**
Characteristic	(N=1685)	(N=995)
Age - yr	82.0 ± 6.5	80.3 ± 6.5
Male sex — no. (%)	600 / 1685 (35.6%)	536 / 995 (53.9%)
STS score†	8.0 ± 6.8	7.9 ± 6.2
Logistic EuroSCORE‡	19.8 ± 11.6	21.6 ± 13.7
NYHA class		
I/II — no./total no. (%)	377 / 1676 (22.5%)	242 / 992 (24.4%)
III/IV — no./total no. (%)	1299 / 1676 (77.5%)	750 / 992 (75.6%)
Coronary artery disease — no./total no. (%)	667 / 1685 (39.6%)	518 / 995 (52.1%)
Previous myocardial infarction — no./total no. (%)	205 / 1685 (12.2%)	197 / 995 (19.8%)
Previous intervention		
CABG — no./total no. (%)	204 / 1685 (12.1%)	226 / 995 (22.7%)
PCI — no./total no. (%)	460 / 1685 (27.3%)	355 / 995 (35.7%)
Balloon aortic valvuloplasty — no./total no. (%)	128 / 1685 (7.6%)	66 / 995 (6.6%)
Cerebral vascular disease — no./total no. (%)	191 / 1685 (11.3%)	143 / 995 (14.4%)
Peripheral vascular disease — no./total no. (%)	248 / 1684 (14.7%)	320 / 995 (32.2%)
COPD		
Pulmonary Artery Disease COPD — no./total no. (%)	327 / 1684 (19.4%)	218 / 995 (21.9%)
Pulmonary Artery Disease Oxygen Dependent — no./total no. (%)	31 / 1684 (1.8%)	11 / 995 (1.1%)
Creatinine > 2 mg/dL (177 µmol/liter) — no./total no. (%)	104 / 1681 (6.2%)	114 / 994 (11.5%)
Atrial fibrillation — no./total no.	395 / 1678 (23.5%)	289 / 990 (29.2%)
Permanent pacemaker — no./total no. (%)	170 / 1685 (10.1%)	134 / 995 (13.5%)
Pulmonary hypertension — no./total no. (%)	440 / 1684 (26.1%)	204 / 995 (20.5%)
Frailty§ — no./total no. (%)	896 / 932 (96.1%)	548 / 579 (94.6%)
Extensively calcified aorta — no./total no. (%)	71 / 1684 (4.2%)	103 / 995 (10.4%)
Chest-wall deformity — no./total no. (%)	52 / 1685 (3.1%)	27 / 995 (2.7%)
Liver disease — no./total no. (%)	18 / 1684 (1.1%)	6 / 995 (0.6%)
Echocardiographic findings		
Aortic-valve area — cm^2	0.7 ± 0.21	0.7 ± 0.21
Mean aortic-valve gradient — mmHg	49.2 ± 16.54	45.0 ± 15.43
Mean LVEF — %	55.1 ± 12.48	53.2 ± 12.50
Moderate or severe mitral regurgitation** — no./total no. (%)	345 / 1633 (21.1%)	174 / 976 (17.8%)

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. AT denotes as treated population, CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve implantation.
† 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.
‡ The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), which measures patient risk at the time of

	Transfemoral	TA/TAo Pooled
cardiovascular surgery, is calculated with the use of a logistic-regression equation. Scores range from 0% to 100%, with higher scores indicating greater risk. A logistic EuroSCORE higher than 20% indicates very high surgical risk. § Frailty was determined by the surgeons according to prespecified criteria. ** Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.		

Table 26: SOURCE XT (High Risk) Clinical Outcomes[a] at 30 days and 1 year (AT Population)*

	30 Days		1-Year	
	Transfemoral	**TA/TAo**	**Transfemoral**	**TA/TAo**
Outcome	**(N=1685)**	**(N=995)**	**(N=1685)**	**(N=995)**
All Cause Death	71 (4.2%)	96 (9.7%)	248 (15.0%)	266 (27.0%)
Cardiac Death	28 (1.7%)	51 (5.2%)	106 (6.7%)	132 (14.4%)
Stroke				
All Stroke	56 (3.4%)	39 (4.1%)	90 (5.6%)	66 (7.6%)
Major Stroke	34 (2.0%)	27 (2.8%)	55 (3.5%)	44 (5.0%)
Repeat hospitalization[b]	80 (4.9%)	83 (9.0%)	396 (25.5%)	314 (36.7%)
Myocardial Infarction	7 (0.4%)	9 (0.9%)	23 (1.5%)	21 (2.5%)
Major Vascular Complications	132 (7.9%)	43 (4.4%)	139 (8.3%)	52 (5.5%)
Renal Failure[d]/AKI	197 (11.9%)	270 (28.0%)	240 (14.7%)	292 (30.6%)
Life-threatening bleeding[c]	63 (3.8%)	84 (8.6%)	74 (4.5%)	101 (10.6%)
Endocarditis	2 (0.1%)	2 (0.2%)	15 (1.0%)	10 (1.2%)
New Atrial Fibrillation	54 (3.3%)	83 (8.8%)	89 (5.6%)	109 (12.0%)
New pacemaker	145 (8.7%)	105 (10.8%)	165 (10.0%)	120 (12.7%)

* AT= As Treated, TAVR = transcatheter aortic valve replacement. Data presented as n (%) of patients where % is the Kaplan-Meier event rate at 30-days and 1-year respectively.
a. CEC adjudicated
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Disabling bleeding: Fatal bleeding OR bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood of packed red blood cells (RBC) transfusion ≥4 units
d. Renal failure is defined as stage III acute kidney injury: Increase in serum creatinine to ≥300% (3 x increase compared with baseline) or serum creatinine of ≥ 4 mg/d (≥354 μmol/L) with an acute increase of at least 0.5 mg/dl (44 μmol/L)

The totality of the SOURCE XT Registry data has demonstrated a beneficial treatment effect for the SAPIEN XT THV for symptom relief, improved physical activity, and quality of life in high surgical risk patients. These beneficial effects outweigh the risks of the procedure; and when taking into account the totality of the risks and outcomes of other available treatment options for high surgical risk patients with critical aortic stenosis (e.g., the currently approved SAPIEN THV and SAVR), the SAPIEN XT THV is a safe and effective option. As such, it is appropriate to leverage post-market SOURCE XT Registry data to provide the scientific evidence in support of the safety and effectiveness of the SAPIEN XT THV in the high risk patients.

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

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Clinical data from the randomized trial in the inoperable patients demonstrate that the SAPIEN XT THV (23 mm and 26 mm) is non-inferior to the previously approved SAPIEN THV in terms of the composite primary endpoint of all-cause mortality and/or major stroke and/or rehospitalizations for symptoms of aortic stenosis and/or complications of the valve procedure at one year for the pooled ITT population.

Clinical data collected through non-randomized registries of the 29 mm SAPIEN XT THV in inoperable patients show that the patient outcomes were consistent with those of the 23 mm and 26 mm SAPIEN XT THVs.

Clinical data collected through non-randomized registries of all three sizes of the SAPIEN XT THV in high surgical risk patients show that the patient outcomes were consistent with those seen in the PARTNER 1A (high risk cohort) trial of SAPIEN THV.

In addition, clinical data have demonstrated that patients undergoing treatment with the SAPIEN XT THV will have a reasonable assurance of achieving hemodynamic, functional, and quality of life benefits similar to those treated with the already approved SAPIEN THV.

B. Safety Conclusions

The results of the pre-clinical laboratory studies demonstrated that the SAPIEN XT THV has acceptable hemodynamic and durability performance, is biocompatible and is suitable for long term implant.

There are potential risks associated with use of the device, including procedure related complications, e.g., death, stroke, major vascular complications, bleeding, conduction disturbance requiring new pacemaker and renal failure, as summarized in Tables 14, 18, 22 and 26. The event rate is consistent between devices and is consistent with past studies using the SAPIEN THV in similar patient populations. The number and severity of risks is well accepted by the patient populations being treated.

C. Benefit-Risk Conclusions

The overall benefit/risk profile of the SAPIEN XT THV is similar to that of the SAPIEN THV; and the probable benefits of the device outweigh the probable risks in a significant portion of the intended patient population. In particular, the SAPIEN XT THV will have one additional valve size available and have better procedure outcomes and reduced vascular complication rate.

D. Overall Conclusions

The totality of the preclinical and clinical studies submitted in the PMA application provides reasonable assurance that the SAPIEN XT THV is safe and effective for the treatment of patients with symptomatic heart disease due to severe native calcific aortic stenosis and with native anatomy appropriate for the 23, 26, or 29 mm valve system, who are judged by a heart team, including a cardiac surgeon, to be inoperable or at high risk (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days) for open surgical therapy.

XIII. CDRH DECISION

CDRH issued an approval order on June 16, 2014. The final conditions of approval cited in the approval order are described below.

1. ***PAS****: Continued follow-up of the IDE inoperable patients cohort (Cohort B)*: The applicant has agreed to a study outline on June 5, 2014 (email) in addition to Revision 6.0 of the IDE protocol (G090216). The study objective is to characterize the safety and effectiveness of the SAPIEN XT THV annually from 2 years through 5 years post-procedure. The study will consist of all pivotal and continued access patients who are currently enrolled, alive and received the device in Cohort B, including nested registries NR1, NR4, NR5, and NR6.

   The primary safety and effectiveness endpoint is a non-hierarchical composite of death (all cause), disabling stroke, and re-hospitalization for symptoms of aortic stenosis. The secondary safety and effectiveness endpoint is a non-hierarchical composite of all stroke, major vascular complications and re-intervention.

   Additional safety endpoints to be evaluated include freedom from: major vascular complications, all neurological events (all stroke and transient ischemic attack), myocardial infarction, acute kidney injury, conduction disturbance requiring new permanent pacemaker implantation, atrial fibrillation at each visit, and transfusion. Procedure related complications will be assessed as well.

   Additional effectiveness endpoints include total days alive and out-of-hospital (from date of index procedure), clinical improvement per New York Heart Association (NYHA) Class, clinical improvement in quality of life, clinical improvement per 6

Minute Walk Test, and mean Intensive Care Unit (ICU) and total index procedure hospital length of stay.

All available subjects in the pivotal study and CAP investigation that were used to support the current PMA application will be followed annually to 5 years post implant.

2. ***Surveillance***: The applicant is required to actively participate as a stakeholder and support the operations of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry (TVTR) to ensure that FDA surveillance occurs for the SAPIEN XT device for 5 years. This surveillance should monitor the following: (1) device success (intra-procedure) (2) all-cause mortality, all stroke, life-threatening (or disabling) bleeding, acute kidney injury-stage 3 (including renal replacement therapy), peri-procedural myocardial infarction, repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months; (3) neurological, vascular and quality of life outcomes at 30 days and 12 months; and (4) all-cause mortality, neurological and vascular outcomes annually through 5 year post implantation.

3. ***Enhanced surveillance and monitoring***: In addition to the conditions outlined above, the applicant is required to implement an enhanced surveillance and monitoring plan for the device for the duration of the variance granted by FDA on June 10, 2014 in accordance with 21 CFR 820.1(e)(2). The plan shall include the following: (1) The applicant will provide to FDA quarterly reports of clinical data extracts from the TVTR regarding the procedural assessments, with specific attention to adverse events related to delivery systems and accessories of the SAPIEN XT THV; and (2) The applicant will notify all implanting sites in the U.S. of the enhanced surveillance and monitoring plan, set up a hotline and list it in the labeling for sites to report device quality related issues to you, and provide to FDA quarterly summary reports of such customer complaint data (e.g., in the form of customer experience reports) for all SAPIEN XT THVs, delivery systems and accessories, with a separate chart for each type of device manufactured at the facility covered in the variance.

FDA issued a Warning Letter to Edwards on May 24, 2013 that listed violations observed during an inspection of the firm's manufacturing facility in Draper, UT on January 22 through February 22, 2013. FDA conducted an additional inspection of the same facility on March 3 through April 11, 2014. At the conclusion of that inspection on April 15, 2014, an FDA 483 form was issued, followed by an "Official Action Indicated" (OAI) letter on May 1, 2014. FDA subsequently approved a variance plan on June 10, 2014 that met the requirements set forth in Section 520(f)(2)(A) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. 820(e)(2). The variance plan provided controls for the manufacture, packing, and storage of the SAPIEN XT THV, delivery systems and accessories in lieu of the FDA's prescribed methods, facilities, and controls.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.