SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Aortic valve, prosthesis, percutaneously delivered
Device Trade Name:	Edwards SAPIEN 3™ Transcatheter Heart Valve, model 9600TFX, 20, 23, 26, and 29 mm, and accessories (Edwards Commander™ delivery system, models 9600LDS20, 9600LDS23, 9600LDS26, and 9600LDS29, with crimp stopper and Qualcrimp crimping accessory; Edwards eSheath Introducer Set, models 914ES and 916ES; and Edwards crimper, model 9600CR)
Device Procode:	NPT
Applicant Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P140031
Date of FDA Notice of Approval:	June 17, 2015
Priority Review:	Granted priority review status on January 20, 2015 because the availability of the device is in the best interest of the patients

II. INDICATIONS FOR USE

The Edwards SAPIEN 3 Transcatheter Heart Valve (THV), model 9600TFX, and accessories are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis 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 ≥8% or at a ≥15% risk of mortality at 30 days).

III. CONTRAINDICATIONS

The Edwards SAPIEN 3 THV is contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other

active infections.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Edwards SAPIEN 3 THV labeling.

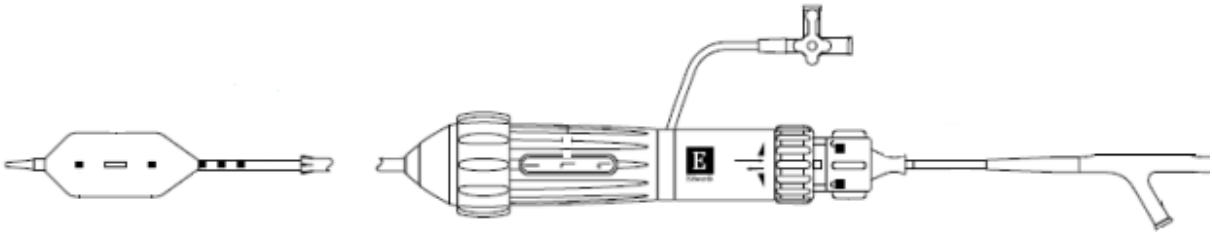
V. DEVICE DESCRIPTION

The Edwards SAPIEN 3 THV, shown in Figure 1, is comprised of a balloon-expandable, radiopaque, cobalt-chromium frame (MP35N), a trileaflet bovine pericardial tissue valve, a polyethylene terephthalate (PET) internal fabric skirt, and a PET external sealing skirt for reduction of paravalvular leakage (PVL).

Figure 1: SAPIEN 3 Transcatheter Heart Valve

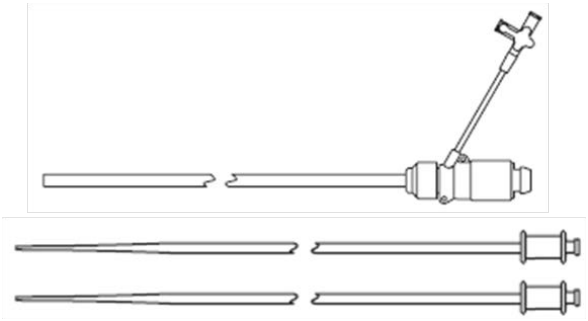
The Edwards Commander delivery system, as shown in Figure 2, includes a handle that provides a flex wheel for articulation of the flex catheter, a tapered tip at the distal end of the delivery system to facilitate crossing the native valve, a balloon catheter for deployment of the THV, and radiopaque markers. The Commander delivery system is used for transfemoral access.

Figure 2: Edwards Commander Delivery System



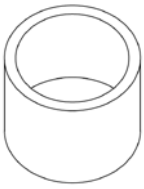
The Edwards eSheath Introducer Set, shown in Figure 3, consists of a sheath and two introducers and is used to facilitate introduction of the SAPIEN 3 THV and accessories into the vasculature.

Figure 3: Edwards eSheath Introducer Set



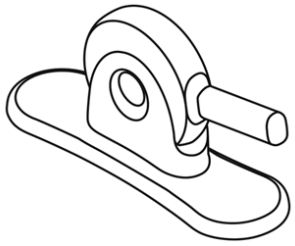
The Qualcrimp crimping accessory, shown in Figure 4, is a non patient-contacting device that is placed around the Edwards SAPIEN 3 THV to protect the leaflets during the crimping process. It is manufactured of tubular polyester polyurethane foam and laminated cylindrically on both the inner and outer surfaces with a polyether urethane material.

Figure 4: Qualcrimp Crimping Accessory



The Edwards Crimper, as shown in Figure 5, 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 is used with a Crimp Stopper (packaged with the Commander delivery system) to correctly crimp the THV.

Figure 5: Edwards Crimper



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for patients with severe symptomatic native aortic valve stenosis who are 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), and 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. Patients should fully discuss these alternatives with their physicians to select the method that best meets their expectations and lifestyle.

VII. MARKETING HISTORY

Commercial distribution of the SAPIEN 3 THV and accessories outside the U.S. began in January 2014. 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 Iceland, Israel, Kuwait, Liechtenstein, Norway, Saudi Arabia, Switzerland, Turkey, and United Arab Emirates. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The adverse effects listed below are associated with access complications associated with standard cardiac catheterization, balloon valvuloplasty, the potential risks of conscious sedation and/or general anesthesia, and the use of angiography:

- 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
- AV fistula or pseudoaneurysm
- Reoperation

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

In vitro studies on the Edwards SAPIEN 3 THV and non-implantable accessories were performed in conformity with ISO 5840: *Cardiovascular Implants-Cardiac Valve Prostheses* (2005).

Biocompatibility Studies

Toxicology and biocompatibility testing for the SAPIEN 3 THV 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 3 THV, Commander delivery system, eSheath Introducer Set, Qualcrimp crimping accessory, and Crimper are provided in Tables 1-5, respectively. Test samples for the studies consisted of all patient-contacting portions of the devices (direct and indirect contact) after all manufacturing processes, including sterilant exposure. All results were acceptable.

Table 1: Summary of Biocompatibility Testing – SAPIEN 3 THV

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 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. No 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.	The test article extracts elicited no reaction at the challenge (0% sensitization), following an induction phase and the test article was classified as having weak allergenic potential.
Irritation/Intracutaneous Toxicity: Rabbit Intracutaneous Reactivity	Determine whether test article extracts would cause local dermal irritation or toxic effects.	The respective test article extracts injection sites did not show significantly greater biological reactions than the sites injected with the control articles.

Test	Purpose	Results
Systemic Toxicity: USP Mouse Systemic Injection	Determine whether test article extracts would cause acute systemic toxicity.	The respective test article extracts did not induce significantly greater biological reactions than the control extracts, when tested in Swiss Albino mice.
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 ≤0.5°C and the test article was considered non-pyrogenic.
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. No abnormalities were observed in any of the implant sites for the test article upon macroscopic gross tissue examination.
Genotoxicity: Reverse Mutation Assay	Determine whether test article extracts would cause mutagenic changes in strains of *S. typhimuruim* and *E. coli*.	Test article extracts did not induce significant increases in the number of revertant colonies as compared to the negative controls under both the activated and non-activated conditions. Non-mutagenic.
Genotoxicity: Chromosomal Aberration Assay	Determine whether test article extracts would cause genotoxicity in Chinese Hamster ovary cells.	Test article extracts did not induce statistically significant increases in the number of structural chromosome aberrations compared to the negative control under both the activated and non-activated conditions.
Genotoxicity: Rodent Bone Marrow Micronucleus	Determine whether test article extracts would cause genotoxic changes as determined by induced micronucleated polychromatic erythrocytes.	Test article extracts did not induce significant increase in micronucleated erythrocytes as compared to negative controls. Non-clastogenic.
Hemocompatibility: Hemolysis	Determine whether the test article would cause hemolysis in vitro and determine the degree of inhibition or promotion of clotting time.	No differences in hemolytic effects observed for both extract and solid samples as compared to negative controls. Material's extract did not adversely affect the clotting time and was determined to be compatible with plasma.
Complement Activation Assay Direct Contact	Determine the potential activation of the complement system in human plasma in response to the test article	Test article was determined to be hemocompatible and not at risk to activate complement. Results equivalent to negative control and untreated plasma.

Table 2: Summary of Biocompatibility Testing – Edwards Commander Delivery System

Test	Purpose	Results
Cytotoxicity: Medium Eluate Method (MEM)	Determine potential biological reactivity of a mammalian cell culture in response to the test article extract.	Test article sample was non-cytotoxic. No reactivity was observed with equivalent results to the negative control.
Hemolysis- Rabbit Blood Direct and Indirect Contact	Determine the potential hemolytic activity on rabbit blood in response to the test article and to its extract	Test article sample was not considered hemolytic. The hemolytic index above the negative control is less than 5%.
Unactivated Partial Thromboplastin Time (UPTT) Assay Indirect Contact	Determine the potential induction of the coagulation of human plasma via measurement of the Unactivated Partial Thromboplastim Time (UPTT), in response to an extract of the test article	Test article sample was not considered to have an effect on the Unactivated Partial Thromboplastin Time (UPTT). No statistically significant decrease between the UPTT of the plasma exposed to the test article and that of the plasma exposed to the negative control.
Complement Activation Assay Direct Contact	Determine the potential activation of the complement system in human plasma in response to the test article	Test article was determined to be hemocompatible and not at risk to activate complement. Results equivalent to negative control.
Salmonella typhimurium and Escherichia coli Reverse Mutation Assay	Determine the potential mutagenicity of the test article extract in various strains of Salmonella typhimurium (S. typhimurium) and Escherichia coli (E. coli) bacteria, via a change in their dependence for histidine or tryptophan.	The test article was considered non-mutagenic. No statistically significant difference between the number of revertant colonies in the test article and that of the negative control.
Systemic Injection Test	Determine the potential for toxic effects of the test article extract as a result of a single –dose systemic injection in mice	Extracts of the test article did not induce a significantly greater biological reaction than the control extracts when tested in Swiss Albino mice.
Rabbit Pyrogen Test (Material Mediated)	Determine the presence of chemical pyrogens in test article extracts by measuring temperature rise in intravenously injected rabbits.	The test article was considered non-pyrogenic. No rabbit showed an individual rise in temperature of 0.5°C or more above the baseline temperature.
Intracutaneous Injection Test	Determine the potential irritation effects of the test article extract as a result of an intracutaneous injection in New Zealand White Rabbits	The test article sites did not show a significantly greater biological reaction than the sites injected with the control article.
Kligman Maximization Test	Evaluate the allergenic potential or sensitizing capacity of the test article.	Test article extracts elicited no reaction at the challenge (0%) sensitization following an induction phase and are classified as having weak allergenic potential.

Table 3: Summary of Biocompatibility Testing – Edwards eSheath Introducer 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. No 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.	All components non-cytotoxic to cells with 0% cell lysis.
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 or 48 hour readings. 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 weight loss or 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.	Temperature rise <0.3ºC and no 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. Results equivalent to negative control.

Table 4: Summary of Biocompatibility Testing – Qualcrimp Crimping Accessory

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. No cell lysis was observed with equivalent results to the negative control.

Table 5: Summary of Biocompatibility Testing – Edwards Crimper

Test	Purpose	Results
Cytotoxicity: Medium Eluate Method (MEM)	Determine whether test article extracts would cause cytotoxicity and cell lysis	Test article sample was non-cytotoxic. No 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.

SAPIEN 3 THV Hydrodynamic Performance

In vitro studies were conducted to evaluate the hydrodynamic performance of the SAPIEN 3 THV 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 ISO 5840: *Cardiovascular Implants-Cardiac Valve Prostheses* (2005). Reference articles for the nominally deployed SAPIEN 3 valve studies consisted of commercially available aortic valves; reference articles for the irregular studies consisted of nominally deployed SAPIEN 3 valves. The matrix of the tests performed and the corresponding results are provided in Table 6.

Table 6: 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 3 Size 20mm, 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, SAPIEN XT size 20mm, 23mm, 26mm, and 29mm, and Perimount Magna size 20mm and 29mm Irregular Test: SAPIEN 3 Size 20mm, 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, SAPIEN XT size 20mm, 23mm, 26mm, and 29mm, and Perimount Magna size 20mm and 29mm	The SAPIEN 3 valve offers acceptable hemodynamics with pressure gradients and effective orifice areas (EOA) that are comparable to those offered by the reference valves.
Steady Backflow Leakage	To determine the leakage rate at various steady back flow pressures.	Nominal Test: SAPIEN 3 Size 20mm, 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, SAPIEN XT size 20mm, 23mm, 26mm, and 29mm, and Perimount Magna size 20mm and 29mm Irregular Test: SAPIEN 3 Size 20mm, 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, SAPIEN XT size 20mm, 23mm, 26mm, and 29mm, and Perimount Magna size 20mm and 29mm	The SAPIEN 3 valve offers satisfactory performance in terms of its competency to prevent significant transvalvular aortic back-flow during the diastolic phase.

Test	Purpose/Objective	Test/Reference Articles	Results
Pulsatile Flow Pressure Drop	To determine pressure drop and effective orifice area performance under pulsatile flow conditions.	Nominal Test: SAPIEN 3 Size 20mm, 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, SAPIEN XT size 20mm, 23mm, 26mm, and 29mm, and Perimount Magna size 20mm and 29mm Irregular Test: SAPIEN 3 Size 20mm, 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, SAPIEN XT size 20mm, 23mm, 26mm, and 29mm, and Perimount Magna size 20mm and 29mm	The SAPIEN 3 valve offers acceptable hydrodynamics with a larger effective orifice area than those required by the ISO 5840:2005 acceptance criteria for aortic valves, and similar pressure drop to the reference valves.
Pulsatile Flow Regurgitation	To determine regurgitation performance under pulsatile flow conditions.	Nominal Test: SAPIEN 3 Size 20mm, 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, SAPIEN XT size 20mm, 23mm, 26mm, and 29mm, and Perimount Magna size 20mm and 29mm Irregular Test: SAPIEN 3 Size 20mm, 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, SAPIEN XT size 20mm, 23mm, 26mm, and 29mm, and Perimount Magna size 20mm and 29mm	The SAPIEN 3 valve offers acceptable hydrodynamics with regurgitant fractions that were lower than those required by the ISO 5840:2005 acceptance criteria.
Flow Visualization	To qualitatively investigate flow characteristics in the vicinity of the valve.	Nominal Test: SAPIEN 3 Size 20mm, 23mm Reference: SAPIEN XT size 20mm, 23mm, and Perimount Magna size 20mm Irregular Test: Irregular SAPIEN 3 size 20mm, 23mm Reference: Nominal SAPIEN XT size 20mm, 23mm, and Perimount size 20mm	The SAPIEN 3 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 3 valves, with no retrograde jet-like flow.
Verification of Bernoulli	To determine whether the Bernoulli	Nominal Test: SAPIEN 3 Size 20mm,	Pressure drop results for the SAPIEN 3 valve

Test	Purpose/Objective	Test/Reference Articles	Results
Relationship	relationship applies to clinical pressure drop measurements.	23mm, 26mm & 29mm Reference: SAPIEN size 26mm <u>Irregular</u> Test: Irregular SAPIEN 3 Size 20mm, 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 26mm	demonstrated correlation with the Bernoulli relationship.

<u>SAPIEN 3 THV Structural Performance</u>

The *in vitro* structural performance studies of the SAPIEN 3 THV were conducted in accordance with 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. The matrix of tests performed and the corresponding results are provided in Table 7.

Table 7: Structural Performance Evaluation

Test	Purpose/Objective	Test/Reference Articles	Results
Accelerated Wear	To assess long-term performance of the valve though accelerated wear.	<u>Nominal</u> Test: SAPIEN 3 size 20mm, 23mm, 26mm & 29mm Reference: Nominal SAPIEN size 23mm, 26mm, & Perimount Magna size 21m, 23mm, 27mm & 29mm valves <u>Irregular</u> Test: SAPIEN 3 size 20mm, 23mm, 26mm & 29mm Reference: SAPIEN size 23mm, 26mm, SAPIEN XT size 20mm, 23mm, 26mm, 29mm & Perimount Magna size 21mm, 23mm, 27mm & 29mm valves	All valves survived durability testing to 200 million cycles in accelerated wear testers without excessive structural damage and/or functional impairment. After testing to 200 million cycles, all valves met the minimum EOA and Total Regurgitation Fraction requirements of ISO 5840:2005.
Dynamic Failure Mode	To obtain information about the failure modes affecting the durability of the valve.	Test: SAPIEN 3 size 20mm, 23mm, 26mm & 29mm Reference: SAPIEN XT size 20mm, 23mm, 26mm, and 29mm Perimount Magna Size 21mm, 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 3 frames size 20mm 23mm, 26mm & 29mm	Minimum force required to compress the frame was acceptable.

Test	Purpose/Objective	Test/Reference Articles	Results
Frame Corrosion Resistance	To characterize the corrosion resistance of the valve frames and 4-hole bars in accordance with ASTMF2129-08	Test: SAPIEN 3 frames size 20mm, 23mm, 26mm & 29mm, Reference: SAPIEN frames size 23mm, 26mm and SAPIEN XT size 26mm	Corrosion resistance of SAPIEN 3 frames are equivalent to the commercially available valve frames.
Frame Fatigue	To determine frame fatigue resistance to 600 million cycles.	Test: SAPIEN 3 frames size 20mm, 23mm, 26mm and 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 the 26mm SAPIEN 3 frame.	Results indicate that the worst-case 26mm SAPIEN 3 frame should not fracture for 600 million cycles, even under the unlikely simultaneous combination of all the worst-case conditions.

SAPIEN 3 THV Design Specific Performance Studies

Design specific *in vitro* performance studies of the SAPIEN 3 THV were completed based on recommendations in the FDA Intravascular Stent Guidance (2010) with acceptable results. The matrix of tests performed and the corresponding results are provided in Table 8.

Table 8: Design Specific Performance Studies

Test	Purpose/Objective	Test Articles	Results
Percent Surface Area	Determination of frame metal surface in contact with native valve leaflets and annulus	N/A – computational analysis	N/A – Characterization testing
Frame Overexpansion	Verification that the SAPIEN 3 frames can withstand an acceptable amount of overexpansion before fracture	SAPIEN 3 frames: sizes 20mm, 23mm, 26mm, and 29mm	PASS - Frames withstood expansion beyond expected over-deployment for an acceptable safety margin
Frame Foreshortening and Recoil	Determination of expected foreshortening and recoil of the SAPIEN 3 THV when passed through compatible sheaths and deployed with the Commander delivery system	SAPIEN 3 valves: sizes 20mm, 23mm, 26mm, 29mm	N/A – Characterization testing
Frame Radial Strength	Determination of the radial strength and characterization of the stiffness of the SAPIEN 3 frame	SAPIEN 3 frames: sizes 20mm, 23mm, 26mm, and 29mm	Radial strength: PASS - All sizes were within specifications Radial Stiffness: N/A – Characterization Testing

Test	Purpose/Objective	Test Articles	Results
Migration Resistance	Verification that the migration resistance of SAPIEN 3 THV under simulated *in vitro* conditions is sufficient to maintain frame/annulus contact	SAPIEN 3 valves: sizes 20mm, 23mm, 26mm, 29mm	PASS - All sizes exhibited acceptable migration
Radiopacity	To visualize the SAPIEN 3 THV under *in vitro* fluoroscopy and x-ray testing conditions.	SAPIEN 3 valves: sizes 20mm, 23mm, 26mm, 29mm	PASS - Radiopaque utilizing fluoroscopic and x-ray modalities

SAPIEN 3 THV Magnetic Resonance Imaging (MRI) Compatibility

The SAPIEN 3 THV has been determined to be MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 tesla or 3 tesla
- Maximum spatial gradient field of 2500 gauss/cm (25 T/m) or less
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (Normal Operating Mode)

Delivery System and Accessory Performance Testing

Performance testing was completed for the Commander delivery system, eSheath Introducer Set, Qualcrimp, and Crimper in accordance with ISO 25539-1:2009, ISO 10555-1:2014, and ISO 11070:1998, with acceptable results. The testing is summarized in Table 9.

Table 9: Delivery System and Accessory Performance Studies

Test	Purpose/Objective	Test Articles	Results
Visual and Dimensional Inspection	Verification that the manufacturing processes produce finished devices meeting design requirements for dimensions, and that the device surfaces are free from defects and extraneous matter.	Commander delivery system: sizes 20mm, 23mm, 26mm, and 29mm eSheath Introducer Set: sizes 14F and 16F Crimper Qualcrimp Crimping Accessory/Crimp Stoppers	PASS - Delivery systems and accessories met design requirements and acceptance criteria for dimensional and visual inspection.
Simulated Use	Verification that the devices perform as intended when subjected to the following simulated use testing: radiopacity, delivery system tracking, guidewire compatibility, torque and kink testing, hemostasis, sheath expansion, crimper durability	Commander delivery system: sizes 20mm, 23mm, 26mm, and 29mm eSheath Introducer Set: sizes 14F and 16F	PASS - Delivery systems and accessories met design requirements and acceptance criteria for simulated use.

Test	Purpose/Objective	Test Articles	Results
		Crimper Qualcrimp Crimping Accessory/Crimp Stoppers	
Balloon Performance	Verification that the Commander delivery system balloon functions as intended when subjected to the following testing: inflation/deflation, inflation pressure, burst pressure, balloon fatigue, deployed balloon dimensional inspection.	Commander delivery system: sizes 20mm, 23mm, 26mm, and 29mm	PASS - The Commander delivery system balloon performs as intended and met acceptance criteria.
THV Interaction	Verification that the Commander delivery system and accessories are compatible with the SAPIEN 3 THV when used as intended. Testing included the following: crimping force, push force through sheath, THV alignment and fine adjustment, THV retention on delivery system, valve retrieval into sheath, deployed valve OD.	SAPIEN 3 valves: sizes 20mm, 23mm, 26mm, 29mm Commander delivery system: sizes 20mm, 23mm, 26mm, and 29mm eSheath Introducer Set: sizes 14F and 16F Crimper Qualcrimp Crimping Accessory/Crimp Stoppers	PASS - Delivery systems and accessories are compatible with the SAPIEN 3 THV and met design requirements and acceptance criteria.
Bond Strength	Verification that the bonds and tubing of the Commander delivery system and eSheath introducer set remain intact when subjected to tensile testing and/or simulated use.	Commander delivery system: sizes 20mm, 23mm, 26mm, and 29mm eSheath Introducer Set: sizes 14F and 16F	PASS - All bonds met design requirements and acceptance criteria.

Sterilization

The SAPIEN 3 THV is sterilized by terminal liquid sterilization (TLS) in buffered glutaraldehyde solution. The Commander delivery system, eSheath Introducer Sheath Set, Qualcrimp crimping accessory, and Crimper are sterilized by ethylene oxide (EO). After sterilization, the devices are held in quarantine until sterility is verified per process specifications. The TLS and EO processes have demonstrated Sterility Assurance Levels (SAL) of 10^{-6} in validation studies.

Packaging and Shelf Life

The packaging for the SAPIEN 3 THV consists of a 3.8 oz jar, a lid and gasket closure system, and shelf and shipping containers.

The Commander delivery system, eSheath Introducer Sheath Set, Qualcrimp crimping accessory, and Crimper are packaged in Tyvek pouches and shelf and shipping cartons.

The labeled shelf life is one (1) year for the SAPIEN 3 THV based on real-time aging, one (1) year for the eSheath Introducer Sheath Set and the Crimper based on accelerated aging, and two (2) years for the Commander delivery system and the Qualcrimp accessory based on accelerated aging. Packaging and product integrity studies were conducted to ensure that the components meet specifications throughout the stated shelf life.

B. Animal Studies

Three chronic animal studies were performed on the SAPIEN 3 THV: two to evaluate the *in vivo* functional performance of the valve (one at 20 and one at 40 weeks post implantation), and one to evaluate the thrombogenic potential of the PVL skirt at three weeks post implantation. The THVs were implanted using an open heart procedure, but were deployed using a delivery system for simulated use. The endpoints of the animal study are functions of valve design and material interactions; therefore, the results of the study are applicable to all valve sizes. An overview of these studies is provided in Table 10.

Table 10: Chronic Animal Study Overview

GLP Chronic 20 Week Study	
Sample Size/Animal Model	21 adult 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	16 size 23 mm SAPIEN 3 THV (Group A had a one time 10-second crimp, Group B had a three time 5-second crimp); 16 NovaFlex 4 (Commander) Delivery System and 15F sheath.
Control Articles	Five (5) commercially available, size 23mm SAPIEN THV (model 9000TFX); five (5) 23F RetroFlex 3 Delivery System and Introducer Sheath.
Technique	Open heart implant of valve in the aortic position under direct visualization within a modified aortic root (modified Cosgrove-Edwards Annuloplasty band/ring sutured into the aortic annulus).
Results	21 open heart implantations were performed; 12 test animals and 3 control animals were sacrificed at 20 weeks. The test and control valves met the acceptance criteria. Early deaths: One control animal died less than 24 hours post procedure due to cardiac complications unrelated to the implanted valve. Four (4) test animals and 1 control animal were removed from the study since the additional animals were not necessary to fulfill the intended sample size and reassigned to the 40 week study described below.

Conclusion	The SAPIEN 3 valve performance was comparable to that of the SAPIEN control valve. The two groups of the SAPIEN 3 and the SAPIEN control met the acceptance criteria and exhibited no embolism, structural valve deterioration, sewing ring dehiscence, material wear, thrombus, significant vegetative growths, significant calcification or significant leaflet damage. Similar healing response (including normal inflammation), tissue overgrowth and good suture integrity were observed in both test and control articles.
Non-GLP 40 week Chronic Animal Study	
Sample Size/Animal Model	Five (5) adult sheep
Test Articles	Four (4) size 23mm SAPIEN 3 THV (2 Group A experienced a one time ten second crimp, 2 Group B experienced a three time five second crimp); four (4) NovaFlex 4 (Commander) Delivery System and 15F sheath.
Control Articles	One (1) size 23 mm SAPIEN THV; one (1) 23F RetroFlex 3 Delivery System and Introducer Sheath.
Technique	Open heart implant of valve in the aortic position under direct visualization within a modified aortic root (modified Cosgrove-Edwards Annuloplasty band/ring sutured into the aortic annulus).
Results	Five (5) open heart implants were performed; Four (4) test animals and one (1) control were sacrificed at 40 weeks. No early deaths or early euthanasia. Pericardial leaflets in the implanted devices showed varying degrees of collagen degeneration, which has been reported in pericardial prosthetic leaflets following implantation historically. This observation was not associated with calcification or any gross or hemodynamic performance changes.
Conclusion	The performance of the SAPIEN 3 valve was comparable to that of the SAPIEN control valve. Both the SAPIEN 3 and the SAPIEN valves met the acceptance criteria and exhibited no embolism, structural valve deterioration, sewing ring dehiscence, material wear, thrombus, significant vegetative growths, significant calcification or significant leaflet damage. Similar healing response (including normal inflammation), tissue overgrowth and good suture integrity were observed in both test and control articles.
Non-GLP 3 Week Study	
Sample Size/Animal Model	Four (4) young adult sheep (9-12 months old, 54-64 kg)
Test Articles	Three (3) 23mm SAPIEN 3 THV (each was crimped three times with a minimum of a 5-second hold); three (3) NovaFlex 4 Delivery System with a sheath and loader kit
Control Articles	One (1) Cribier-Edwards 23 mm SAPIEN THV; one (1) RetroFlex 3 Delivery System and Introducer Sheath
Technique	Open heart implant of valve in the aortic position under direct visualization within a modified aortic root (modified Cosgrove-Edwards Annuloplasty band/ring sutured into the aortic annulus). The modified Cosgrove-Edwards Annuloplasty band used in this study had added irregularities to model calcific nodules.

Results	Four (4) open heart implants were performed; three (3) test animals and one (1) control were explanted at 3 weeks. No early deaths or early euthanasia. The modified Cosgrove ring was successful at producing paravalvular leak. Both test and control valves healed normally with pliable leaflets, and without coronary occlusion, material wear, leaflet retraction, or calcification. One test valve had mild to moderate vegetations at all 3 commissures on the inflow aspect. The presence of vegetations was an incidental finding and not indicative of endocarditis or other pathologic condition. No valve had thrombus on the primary area of interest, the PVL skirt. One test valve had single area of moderate pink tan thrombus deposition on sewing band leaflet interface of the non-coronary cusp on the outflow aspect. The material was firmly adhered to the underlying cloth and was considered to be mature (chronic) fibrin thrombus.
Conclusion	All valves healed normally and there was no evidence of thrombus deposition on the PVL skirt or thrombus with embolic potential at any other location on the valves. This was comparable to the control results.

The results of these studies demonstrated that the SAPIEN 3 THV has acceptable hemodynamic, healing and durability performance and is suitable for long-term implant. Further summaries of these studies are provided in Table 11.

Table 11: Chronic Animal Study Summaries

Evaluation Parameter	Summary of Results
GLP Chronic 20 Week Study	
Clinical History and Hematology	One control (SAPIEN) animal was found dead the morning after surgery. The cause of death at explant was suspected to be due to a new acute infarct or an arrhythmia from an infarct at surgery. Some degree of valve oversizing was suspected, as shown by bruising of the annulus at the anterior mitral leaflet. This animal died unexpectedly and was not weighed at explant. The animal was disqualified from the study. The cause of death was non-device related. Hematologic findings were largely unremarkable at implant and explant and were comparable between both test and control groups. At explant, plasma free hemoglobin results were, in most instances, similar or lower than those at implant. At explant, Haptoglobin results were, on average, slightly higher at explant than implant for all three groups. Both test and control devices were hemocompatible. There were no other indicators of on-going hemolysis, such as anemia. There was no evidence of thromboembolic complications.

Hemodynamic Performance	In general, peak gradients and cardiac outputs at explant tended to be higher than at implant. One control animal and seven test animals had evidence of valvular insufficiency by contrast angiography which corresponded with the gross finding of paravalvular gaps on gross exam. The gaps were located between the annuloplasty ring and the native annulus, and were a failure of the model and not a problem with the valve delivery or performance. Values for the average cardiac output, peak gradient post implant, and the average peak gradient with an induced cardiac output were consistent with improved cardiac function compared to immediately post-bypass. At explant the test valves and control valves were comparable for aortic insufficiency. Two valves in each group had no leak, three valves from the test groups and one in the control group had trace to mild leak, and one valve in the test group had moderate to severe leak.
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 control and test groups at 20 weeks. There were no thrombus, valvular mineralization and vegetative growths in the valves of either the control or test groups. There was no migration, leaflet damage, material wear, or structural failure in the valves. Only two animals (one from the control group and one from the test group) had minimal to mild calcification deposits on gross exam. The gross examination for the target organs (kidneys, liver, spleen, lung) were similar between the test and control groups, and were all within normal limits.
Non-GLP 40 week Chronic Animal Study	
Clinical History and Hematology	All five animals (four tests and one control) were clinically normal prior to explant at 40 weeks. There were no early deaths. All animals were free of adverse clinical signs and displayed normal behavior and vital signs throughout the implant period. Findings were comparable between the test and control groups. None of the pre-implant and pre-explant abnormal hematology findings was considered to be clinically significant to affect the outcome of the study. Both test and control devices were hemocompatible. There were no indicators of on-going hemolysis, such as anemia, and no evidence of thromboembolic complications.
Hemodynamic Performance	In general, the peak gradients and cardiac outputs at explant tended to be higher than those at implant. This observation was consistent with improved cardiac function, as compared to what would be anticipated immediately post-bypass, and was similar to other prosthetic heart valves tested in the past. Though angiography data could not be located for one animal, gross necropsy did not find any paravalvular gaps, leaflet damage or retraction, suggesting no leak would have been observed on fluoroscopy.

Histopathology	Histopathology results showed no apparent differences in tissue reactions (general healing, calcification, or morphology of the tissue/valve interface) between the test devices and the control device. Tissue reactions were generally of low severity and were considered to be typical of this type of devices.
Gross Observations	General healing results were comparable among valve types at 40 weeks. All valves had pliable leaflets and had no thrombus, coronary occlusion, material wear, frame fracture or valve migration. All had good suture integrity. The valves were securely seated with normal healing into the aortic root. Three test animals had minimal to moderate paravalvular space. One test animal and the control animal had minimal vegetative growths. One test animal had a small leaflet perforation, likely caused by a nearby elongated suture, and the control animal had minimal to moderate leaflet retraction on two leaflets, possibly from calcification. The gross examination for the target organs (kidneys, liver, spleen, lung) were similar between the test and control groups, and were all within normal limits.
Non-GLP 3 Week Study	
Clinical History and Hematology	All four animals (three tests and one control) were clinically normal prior to explant at 3 weeks. There were no early deaths. The pre-implant and pre-explant hematology findings were unremarkable, and were comparable between the control and test groups.
Hemodynamic Performance	Intracardiac (ICE) or transthoracic (TTE) echocardiography was performed immediately post-implant and immediately prior to explant. Aortic insufficiency or paravalvular leaks (PVL), integrity of the subvalvular structures (chordae and papillary muscles) and mitral valve regurgitation (MR) were evaluated and recorded. All three test animals had paravalvular spaces located near cable ties which were affixed to the rings to intentionally facilitate PVL between the ring and the skirt to simulate a worst-case condition for thrombus formation; in two of the animals the gap was near the left coronary cusp, and in the third the gap was near the non-coronary cusp. At explant, no valve had thrombus on the skirt (the primary area of interest).
Histopathology	Histopathology results showed no apparent differences in tissue reactions (general healing, calcification, or morphology of the tissue/valve interface) between the test group valves 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 four animals at 3 weeks with pliable leaflets, no coronary occlusion, material wear, leaflet retraction, or calcification. Two of the test articles had no thrombus or vegetations. One test article had a single area of moderate pink tan thrombus deposition on the sewing band leaflet interface of the non-coronary cusp on the outflow aspect. The material was firmly adhered to the underlying cloth and was considered to be mature (chronic) fibrin thrombus. No valve had thrombus on the primary area of interest, the PVL skirt.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study in the U.S. to establish a reasonable assurance of safety and effectiveness of transcatheter aortic valve replacement with the Edwards SAPIEN 3 THV in patients with severe native calcific aortic stenosis under IDE G090216 (entitled the "PARTNER II" trial). The pooled data from two separate cohorts of the clinical study, i.e., the PIIS3HR cohort and Nested Registry #7 (NR7), were the basis for the PMA approval decision. A summary of the clinical study is presented below.

Note that both the Edwards Commander delivery system (for transfemoral [TF] access) and the Edwards Certitude delivery system (for transapical [TA] or transaortic [TAo] access) were used in the clinical study and the clinical results presented herein include all access routes. However, the Edwards Certitude delivery system is not included in this PMA application.

A. Study Design

The PIIS3HR Cohort of the PARTNER II trial was a single arm, non-randomized, historical-controlled study to compare the third generation Edwards SAPIEN 3 THV system with the first generation Edwards SAPIEN THV system in patients who either have high risk for surgery or cannot undergo surgery (inoperable). The valve sizes used in the PIIS3HR trial included only the 23, 26 and 29 mm sizes. The 20 mm valve size was introduced into the trial after enrollment was completed with the three larger sizes, thus a separate nested registry, NR7, with identical inclusion/exclusion criteria as the PIIS3HR Cohort except for the aortic annulus diameter, was created to collect data for the 20 mm valve. Data from the PIIS3HR cohort and NR7 are pooled for the statistical analyses. For convenience, this combined cohort is referred to as "PIIS3HR" hereafter.

Patients were treated between October 1, 2013 and July 17, 2014. The database reflected data collected through November 21, 2014 and included 583 eligible patients enrolled at 29 investigational sites in the U.S.

The study used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify Edwards Lifesciences of any safety or compliance issues, a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint related events reported during the trial per *a priori* established VARC 2 definitions,[1] an ECG core laboratory for independent analysis of rhythm, and an echocardiographic core laboratory for independently analyzing all echocardiograms.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in PIIS3HR was limited to patients who met the following inclusion criteria:

- STS >8% (a candidate who did not meet the STS score criteria of >8% could be included in the study if a peer review by at least two investigators [excluding the enrolling surgeon] concluded and documented that the patient's predicted risk of operative mortality was ≥ 50%. The surgeon's assessment of operative comorbidities not captured by the STS score had to be documented).
- 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 ≤ 0.80 cm^2 or indexed effective orifice area (EOA) < 0.5 cm^2/m^2. Qualifying echo was required to be within 60 days of the date of the procedure.
- Symptomatic from aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater.
- The heart team agreed (and verified in the case review process) that valve implantation would likely benefit the patient.
- The study patient or the study patient's legal representative was informed of the nature of the study, agreed to its provisions and provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.
- The study patient agreed to comply with all required post-procedure follow-up visits including annual visits through 5 years and analysis close date visits, which were to be conducted as phone follow-up.
- For inoperable patients: The heart team agreed that medical factors precluded operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeded the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity was ≥ 50%. The surgeons' consult notes had to specify the medical or anatomic factors leading to that conclusion and had to 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 was required to physically evaluate the patient. Inoperable patients had to be approved by a member of one of the PARTNER II Leadership Committees.
- Aortic valve annulus area range (273 mm^2 - 680 mm^2) per 3D imaging (echo, CT, or magnetic resonance imaging [MRI]).

Patients were <u>not</u> permitted to enroll in PIIS3HR if they met any of the following exclusion criteria:

- Evidence of an acute myocardial infarction (MI) ≤ 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 (World Health Organization [WHO] definition)].
- Aortic valve was a congenital unicuspid or congenital bicuspid valve, or was non-calcified.
- Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).

- Pre-existing mechanical or bioprosthetic valve in any position.
- Any therapeutic invasive cardiac procedure resulting in a permanent implant that was performed within 30 days of the index procedure. Implantation of a permanent pacemaker or implantable cardioverter defibrillator (ICD) was not considered exclusionary.
- Any patient with a balloon valvuloplasty (BAV) within 30 days of the procedure (unless BAV was a bridge to procedure after a qualifying echo).
- Patients with planned concomitant surgical or transcatheter ablation for atrial fibrillation.
- Leukopenia (white blood cells [WBC] < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), thrombocytopenia (Plt < 50,000 cell/mL).
- Untreated clinically significant coronary artery disease requiring revascularization.
- Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of screening evaluation.
- Need for emergency surgery for any reason.
- Hypertrophic cardiomyopathy with or without obstruction.
- Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20%.
- Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
- Active upper gastro-intestinal (GI) bleeding within 3 months (90 days) prior to procedure.
- A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.
- Native aortic annulus size < 16 mm or > 28mm as measured by echocardiogram.
- Clinically (by neurologist) or neuroimaging confirmed stroke or transient ischemic attack (TIA) within 6 months (180 days) of the procedure.
- Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at the time of screening.
- Estimated life expectancy < 24 months (730 days) due to carcinoma, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease.
- Expectation that patient would not improve despite treatment of aortic stenosis.
- 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. (Transfemoral)
- Iliofemoral vessel characteristics that would preclude safe placement of 14F or 16F introducer sheath such as severe obstructive calcification, severe tortuosity or minimum average vessel size less than 5.5 mm. (Transfemoral)
- Currently participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were

investigational, but had since become commercially available, were not considered investigational trials.
- Known enrollment in the PARTNER I Trial.
- Active bacterial endocarditis within 6 months (180 days) of procedure.

2. Follow-up Schedule

Follow-up periods were discharge or 7 days, whichever comes first, 30 days, 6 months, 12 months, and annually thereafter to a minimum of 5 years post procedure.

3. Clinical Endpoints

The primary endpoint was a non-hierarchical composite of death (all cause), all stroke, and aortic insufficiency (AI) ≥ moderate at 30 days. Stroke was evaluated by the CEC, and AI was assessed by the echocardiography core laboratory. Events occurring on day 30 or earlier were included in the evaluation. The primary hypothesis was as follows:

$$H_0: P_T - P_C \geq 7.5\%$$
$$H_A: P_T - P_C < 7.5\%$$

where P_T denotes the event proportion in the test arm, and P_C denotes the event proportion in the control arm. The test was performed as a one-sided test at $\alpha = 0.05$. The analysis was a non-inferiority analysis adjusted for propensity quintiles.

There were two pre-specified hypothesis-driven secondary endpoints: AI ≥ moderate at 30 days and major vascular complications at 30 days. The hypothesis for each secondary endpoint was as follows:

$$H_0: P_T = P_C$$
$$H_A: P_T \neq P_C$$

where P_T denotes the event proportion in the test arm, and P_C denotes the event proportion in the control arm. The comparison is a two-sided test with $\alpha = 0.05$. The analyses were adjusted for the stratification of propensity quintiles first and then adjusted for the multiplicity.

B. Accountability of the PMA Cohort

All 583 eligible patients were successfully implanted with a SAPIEN 3 THV, which constitutes the Valve Implant (VI) population. Among the VI population, 491 patients were implanted via the TF access route, and 92 patients via the TA or TAo access route, as summarized in Table 12. At the time of database lock, 570 of the 583 VI patients were still alive, and 565 patients had completed the 30-day post-operative visit.

Table 12: Patient Accountability

	Overall	TF	TA /TAo
Eligible Patient Population (EPP)	583	491	92
Valve Implant (VI) Population	583	491	92

Eligible Patient Population (EPP) consists of all enrolled patients who received treatment assignment from the database and entered into the catheterization laboratory/hybrid suite and who remained eligible to receive the implant.
Valve Implant (VI) Population consists of all enrolled patients who received a SAPIEN 3 implant, and retained the valve upon leaving the catheterization laboratory/hybrid suite.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are summarized in Table 13, which are typical of a TAVR study performed in the U.S.

Table 13: Patient Demographics and Baseline Characteristics - PIIS3HR VI Population

Characteristic	Overall (N= 583)	TF (N= 491)	TA/TAo (N= 92)
Age, yr	82.6 ± 8.1	82.8 ± 8.2	81.7 ± 7.5
Male sex, no. (%)	338 (58.0%)	277 (56.4%)	61 (66.3%)
STS score	8.6 ± 3.7	8.4 ± 3.5	10.0 ± 4.3
New York Heart Association (NYHA) class, no. (%):			
I/II	58 (9.9%)	51 (10.4%)	7 (7.6%)
III/IV	525 (90.1%)	440 (89.6%)	85 (92.4%)
Coronary artery disease, no. (%)	444 (76.2%)	360 (73.3%)	84 (91.3%)
Previous myocardial infarction, no. (%)	117 (20.1%)	87 (17.7%)	30 (32.6%)
Previous intervention, no. (%)			
Coronary-artery bypass grafting (CABG)	193 (33.1%)	145 (29.5%)	48 (52.2%)
Percutaneous coronary intervention (PCI)	199 (34.1%)	163 (33.2%)	36 (39.1%)
Prior aortic valvuloplasty	62 (10.6%)	49 (10.0%)	13 (14.1%)
Cerebral vascular accident (CVA), no. (%)	64 (11.0%)	53 (10.8%)	11 (12.0%)
Peripheral vascular disease, no. (%)	205 (35.2%)	155 (31.6%)	50 (54.3%)
Chronic obstructive pulmonary disease (COPD), no. (%):			
Any	259 (44.6%)	216 (44.1%)	43 (47.3%)
Oxygen-dependent	68 (11.8%)	58 (11.9%)	10 (11.0%)
Atrial fibrillation, no. (%)	255 (43.7%)	212 (43.2%)	43 (46.7%)
Permanent pacemaker, no. (%)	95 (16.3%)	78 (15.9%)	17 (18.5%)
Severe pulmonary hypertension, no. (%)	30 (5.1%)	24 (4.9%)	6 (6.5%)
Frailty, no. (%)	180 (30.9%)	162 (33.0%)	18 (19.6%)
Chest deformities that preclude an open chest procedure, no. (%)	4 (0.7%)	3 (0.6%)	1 (1.1%)
Cirrhosis, no. (%)	11 (1.9%)	9 (1.8%)	2 (2.2%)
Echocardiographic findings			
Effective Orifice Area (EOA), cm^2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.1

Characteristic	Overall (N= 583)	TF (N= 491)	TA/TAo (N= 92)
Mean aortic-valve gradient, mmHg	45.5 ± 14.3	45.7 ± 14.4	44.0 ± 13.2
Mean left ventricular ejection fraction (LVEF), %	56.4 ± 14.8	57.0 ± 14.5	53.2 ± 15.9
Moderate or severe mitral regurgitation, no./total no. (%)	69/541 (12.8%)	63/461 (13.7%)	6/80 (7.5%)

Plus–minus values are means ± SD.

D. Safety and Effectiveness Results

1. Primary Endpoint

The composite rate of all-cause mortality, all stroke, and AI ≥ moderate at 30 days was 6.7% in the SAPIEN 3 cohort and 15.6% in the SAPIEN cohort, as shown in Table 14. The resulting proportion difference in the average treatment effect on the treated (ATT; see reference [2]) was -6.9% (90% CI: [-13.3%, -0.5%]). Since the upper limit of the CI was < 7.5%, the non–inferiority was met.

Table 14: Primary Endpoint Analysis – Non-Inferiority Test SAPIEN 3 vs. SAPIEN (PIIS3HR VI Population)

Event at 30 days	SAPIEN 3 (N=583)	SAPIEN (N=326)	Weighted Proportion Difference in Average Treatment Effect on the Treated (ATT)
Composite of Death, Stroke and AI ≥ Moderate)	6.7% [5.1%, 8.6%][1]	15.6% [12.6%, 19.5%][1]	-6.9% [-13.3%, -0.5%][2]

[1]For each individual study, the two-sided 90% stratified Wilson confidence interval was provided.
[2] The Wald-type two-sided 90% confidence interval using weighted mean and SD is provided

The Kaplan-Meier (K-M) estimates for all-cause mortality, cardiac mortality, and all stroke at 30 days for the SAPIEN 3 cohort and the SAPIEN cohort are provided in Table 15.

Table 15: Death and Stroke at 30 Days (SAPIEN 3 vs. SAPIEN VI Population)

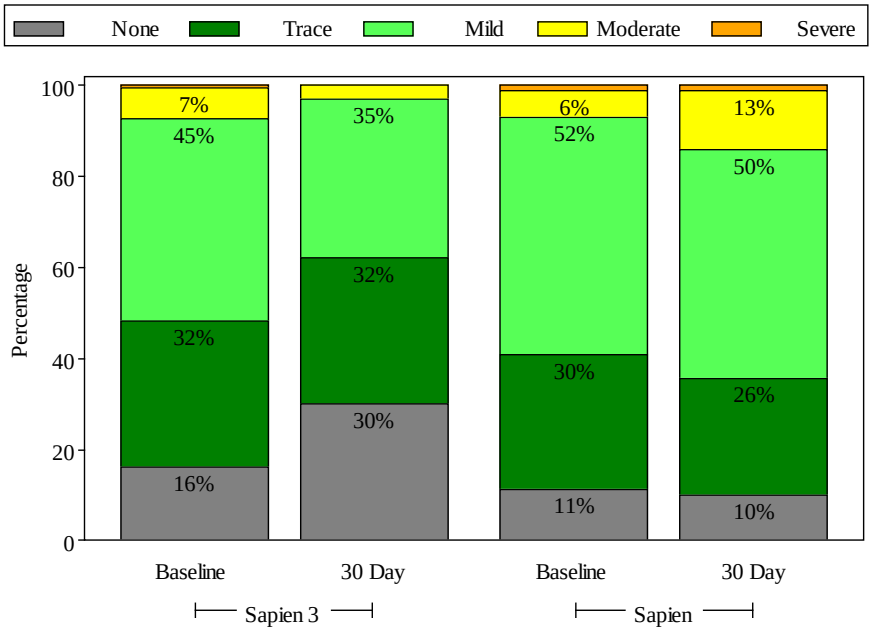
	SAPIEN 3 (N= 583)			SAPIEN (N= 326)		
Event at 30 Days	**No. Events**	**No. Pts with Events**	**K-M Estimated Event Rate[1] (95% CI)**	**No. Events**	**No. Pts with Events**	**K-M Estimated Event Rate (95% CI)**
Death	13	13	2.2% ([1.3%, 3.8%])	15	15	4.6% ([2.8%, 7.5%])
Cardiac Death	8	8	1.4% ([0.7%, 2.7%])	10	10	3.1% ([1.7%, 5.7%])
All Stroke	9	9	1.6% ([0.8%, 3.0%])	14	14	4.3% ([2.6%, 7.2%])

[1]Kaplan-Meier (K-M) estimates at 30 days used time to first event for each patient. Events occurring after 30 days were not included in this analysis.

2. Secondary Endpoints

Aortic insufficiency by visit is provided in Figure 6**.**

Figure 6: Aortic Insufficiency by Visit – SAPIEN 3 vs. SAPIEN (PIIS3HR VI Population)



The proportion of patients with AI ≥ moderate at 30 days was 3.0% in the SAPIEN 3 cohort and 14.3% in the SAPIEN cohort, which were found to be statistically significantly different (p=0.0051; Table 16).

Table 16: Aortic Insufficiency at 30 Days (SAPIEN 3 vs. SAPIEN VI Population)

Event at 30 Days	**SAPIEN 3 (N = 583)**	**SAPIEN (N = 326)**	**Weighted Proportion Difference in Average Treatment Effect on the Treated (ATT)**	**P-value**
AI ≥Moderate, n/Total no. (%) [95% CI]	16/532 (3.0%) [1.7%, 4.8%][1]	40/280 (14.3%) [10.4%, 18.9%][1]	-13.1% [-22.2%, -3.9%][2]	0.0051

[1]95% Clopper-Pearson Exact confidence interval.
[2]The Wald-type two-sided 90% confidence interval using weighted mean and SD is provided.

The rate of major vascular complications at 30 days post implantation is shown in Figure 7. The rate was 5.0% for the SAPIEN 3 cohort and 10.1% for the SAPIEN cohort, which were found to be not statistically significantly different (p=0.0578; Table 17).

Figure 7: Major Vascular Complications at 30 Days – SAPIEN 3 vs. SAPIEN (VI Population)

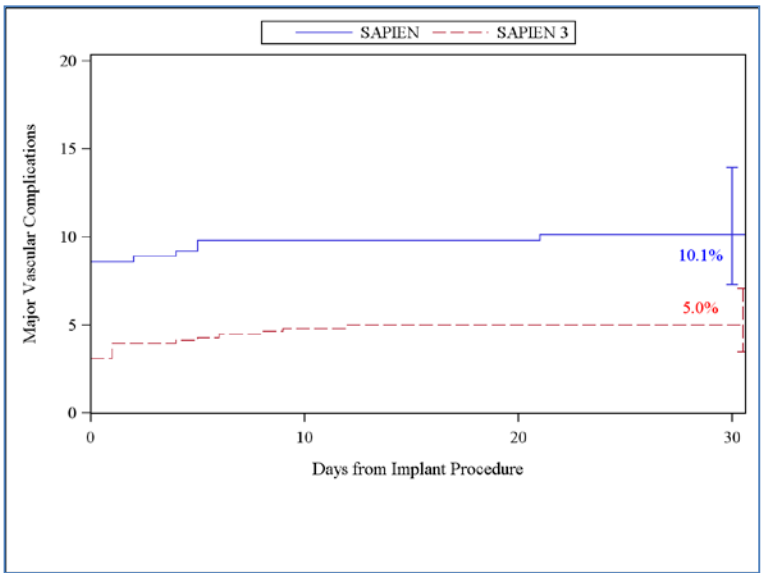


Table 17: Major Vascular Complications at 30 Days (SAPIEN 3 vs. SAPIEN VI Population)

Event at 30 Day	SAPIEN 3 (N=583)	SAPIEN (N=326)	Weighted Proportion Difference in Average Treatment Effect on the Treated (ATT)	P-value
Major Vascular Complications, n/Total no. (%) [95% CI]	29/583 (5.0%) [3.4% , 7.1%]	33/326 (10.1%) [7.1% , 13.9%][1]	-8.0% [-16.2%, 0.3%][2]	0.0578

[1] 95% Clopper-Pearson Exact confidence interval.
[2]The Wald-type two-sided 90% confidence interval using weighted mean and SD is provided.

Table 18 lists the hypothesis testing of the two secondary endpoints conducted with p-values in descending order for the Hochberg multiplicity adjustment steps. The largest p-value (p=0.0578 from major vascular complications) was greater than 0.05. As such, the null hypothesis was not rejected for the testing of major vascular complications at 30 days. The subsequent testing of AI ≥ moderate at 30 days had a p-value of 0.0051, which was less than 0.025. As such, the null hypothesis was rejected for AI ≥ moderate at 30 days, indicating that SAPIEN 3 was superior over SAPIEN in regards to AI ≥ moderate at 30 days.

Table 18: Secondary Endpoints for Labeling (SAPIEN 3 vs. SAPIEN VI Population)

Endpoints	Original p-value	Inference
Major Vascular Complications at 30 Days	0.0578	> 0.05; reject the alternative hypothesis. Proceed to the rest of testing
AI at 30 Days	0.0051	< 0.025; claim superiority

3. Adverse Events

The key CEC adjudicated adverse events at 30 days are presented in Table 19.

Table 19: CEC Adjudicated Adverse Events at 30 Days (PIIS3HR VI Population)

30 Day Adverse Events	Overall	TF	TA/TAo
Composite Event Rate of Death, All Stroke and AI ≥ Moderate, n/N (%)	37/545 (6.8 %)	27/463 (5.8 %)	10/82 (12.2 %)
Death			
From Any cause, n/N (%)	13/583 (2.2%)	8/491 (1.6%)	5/92 (5.4%)
From cardiovascular cause, n/N (%)	8/583 (1.4%)	5/491 (1.0%)	3/92 (3.3%)
Stroke, n/N (%)	9/583 (1.5%)	8/491 (1.6%)	1/92 (1.1%)
AI ≥ moderate, n/N (%)	16/532 (3.0 %)	12/455 (2.6 %)	4 /77 (5.2 %)
Myocardial Infarction, n/N (%)	3/583 (0.5%)	2/491 (0.4%)	1/92 (1.1%)
Major Vascular Complications, n/N (%)	29/583 (5.0%)	26/491 (5.3%)	3/92 (3.3%)
Acute Kidney Injury, Stage III, n/N (%)	6/583 (1.0%)	4/491 (0.8%)	2/92 (2.2%)
Disabling Bleeding Event, n/N (%)	37/583 (6.3%)	27/491 (5.5%)	10/92 (10.9%)
Aortic Valve Re-Intervention, n/N (%)	6/583 (1.0%)	4/491 (0.8%)	2/92 (2.2%)
Endocarditis, n/N (%)	1/583 (0.2%)	1/491 (0.2%)	0/92 (0.0%)
Conduction Disturbance Requiring Permanent Pacemaker, n/N (%)	76/583 (13.0%)	65/ 491 (13.2%)	11/ 92 (12.0%)

4. Other Results

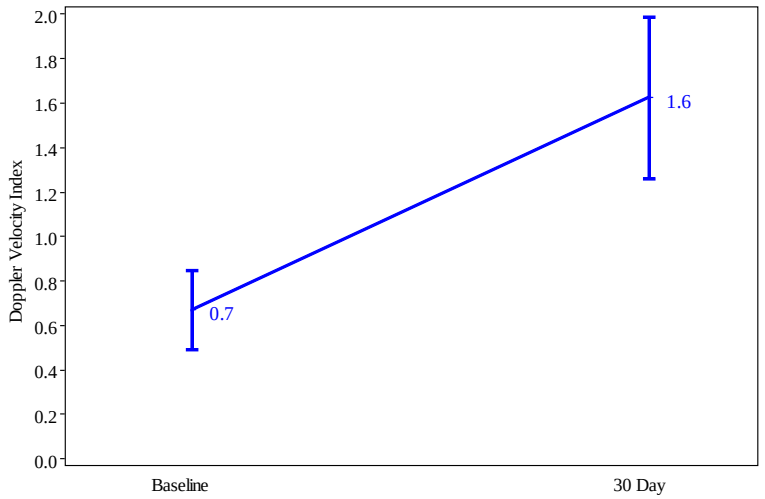
Procedural Information

Overall, the mean duration in the catheterization laboratory/hybrid suite was 192.8 ± 59.3 min, the mean total procedure time was 86.3 ± 44.2 min, and the mean total anesthesia time was 193.7 ± 62.9 min. These duration times were slightly shorter in the TF group. General anesthesia was used in the vast majority of cases; 15.9% of the TF patients had conscious sedation. Correct positioning of the valve was achieved in 99.1% of the patients. Five patients (0.9%; including 3 TF patients) were implanted with a second valve. One patient (0.2%) experienced valve embolization following rupture of the delivery balloon on annular calcium. This patient was converted to surgical aortic valve replacement and later died from aortic dissection.

Valve Performance

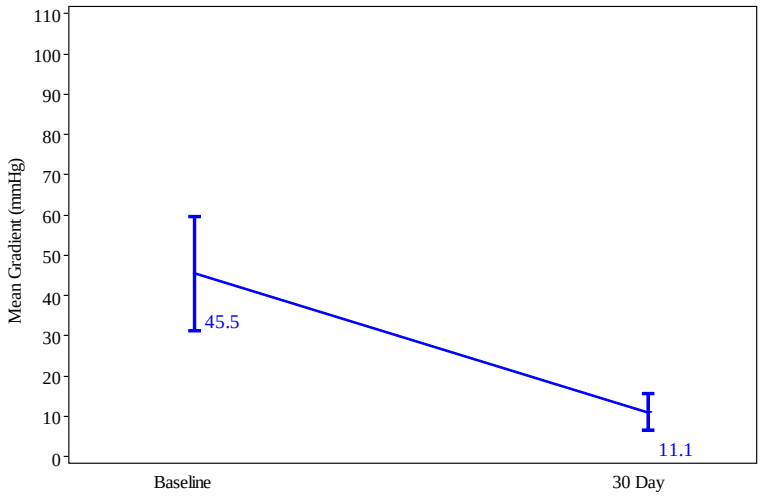
The mean EOA increased from 0.7 ± 0.2 cm^2 at baseline to 1.6 ± 0.4 cm^2 at 30 days, as shown in Figure 8.

Figure 8: Effective Orifice Area (PIIS3HR VI Population)



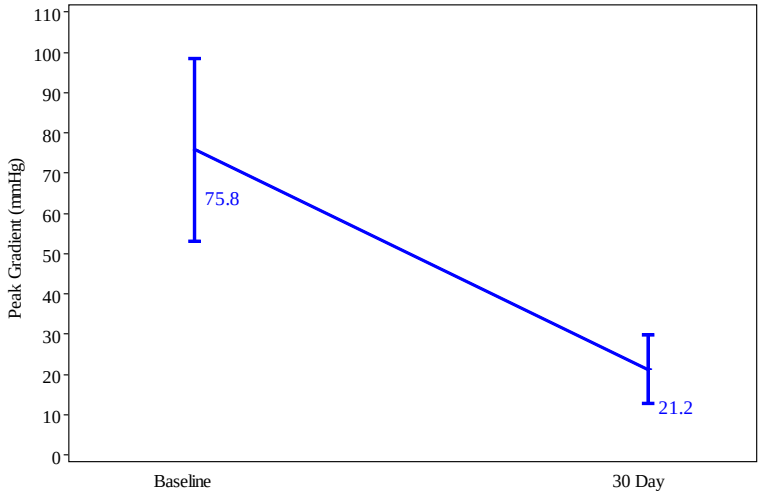
The average mean gradient decreased from 45.5 ± 14.3 mmHg at baseline to 11.1 ± 4.5 mmHg at 30 days, as shown in Figure 9.

Figure 9: Mean Gradient (PIIS3HR VI Population)



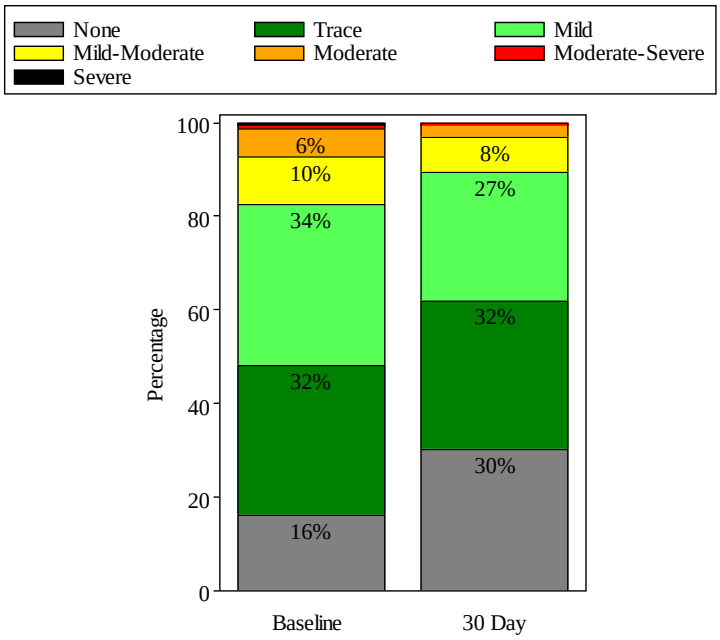
The mean peak gradient decreased from 75.8 ± 22.6 mmHg at baseline to 21.2 ± 8.5 mmHg at 30 days, as shown in Figure 10.

Figure 10: Peak Gradient (PIIS3HR VI Population)



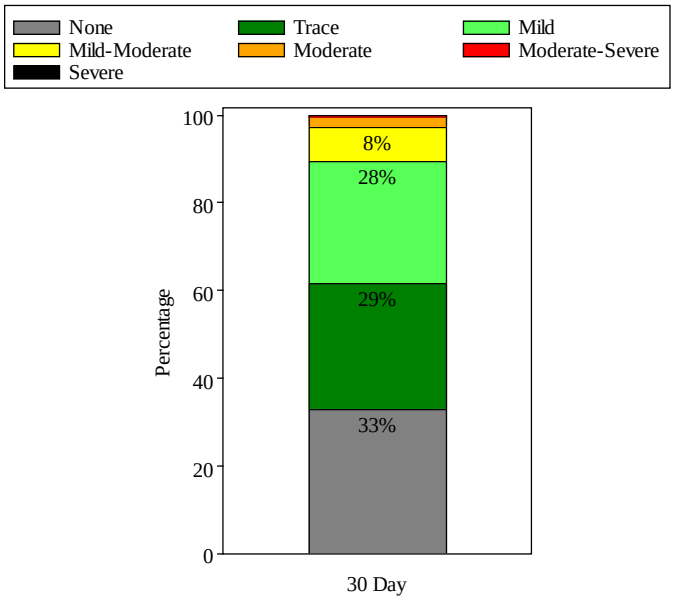
The proportion of patients with AI ≥ moderate was 7.3% at baseline and 3.0% at 30 days, as shown in Figure 11.

Figure 11: Aortic Insufficiency (PIIS3HR VI Population)



The proportion of patients with aortic paravalvular leak (PVL) ≥ moderate was 2.9% at 30 days, as shown in Figure 12**.**

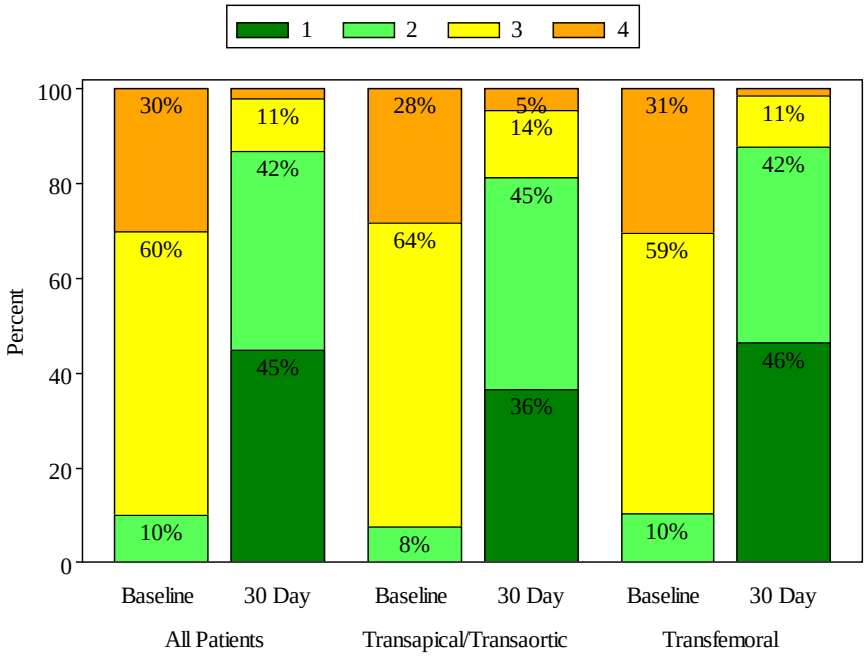
Figure 12: Aortic Paravalvular Leak (PIIS3HR VI Population)



NYHA

The NYHA class by visit is shown in Figure 13. For all patients, the mean NYHA class was 3.2 ± 0.6 at baseline and 1.7 ± 0.7 at 30 days.

Figure 13: NYHA Class by Visit (PIIS3HR VI Population)



Six Minute Walk Test (6MWT)

The improvement in mean 6MWT distance was 38.5 ± 110.2 meters from baseline to 30 days for all patients, 42.6 ± 107.8 meters for all TF patients, and 15.9 ± 121.2 meters for all TA/TAo patients.

Length of Stay (LoS)

The overall mean LoS was 6.8 ± 4.8 days, which included 3.0 ± 2.7 days in the ICU. The mean LoS was 6.1 ± 4.3 days (including 2.7 ± 2.3 days in the ICU) for the TF patients and 10.4 ± 5.4 days (including 4.8 ± 3.9 days in the ICU) for the TA/TAo patients.

Quality of Life (QoL)

QoL was measured using the visual analog scale (VAS) of the EuroQoL (EQ-5D) measure. The VAS is a self-assessment in which patients rate their well-being on a scale from 0 to 100 where 0 is the worst state they can imagine and 100 is the best state. During the trial, the mean improvement in VAS scale from baseline to 30 days was 14.6 ± 22.2 for all patients, 15.1 ± 21.5 for the TF patients, and 11.5 ± 25.7 for the TA/TAo patients.

Additional QoL instruments

The mean overall Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score was 46.9 ± 22.6 at baseline, and 67.5 ± 22.6 at 30 days for the entire VI population. Except for self-efficacy which showed a small improvement, moderate to large improvements were observed in all other subscores at 30 days. In general, improvements in the TF group were slightly larger compared to those observed in the TA/TAo group.

Using the SF-36 norm based questionnaire, the physical component score for all patients improved from 32.0 ± 8.9 at baseline to 37.1 ± 9.7 at 30 days, and the mental component score improved from 46.9 ± 12.8 at baseline to 50.0 ± 12.5 at 30 days. In the TF group, the physical component score improved from 31.8 ± 8.7 at baseline to 37.3 ± 9.8 at 30 days, and the mental component score improved from 46.8 ± 13.1 at baseline to 50.5 ± 12.2 at 30 days. In the TA/TAo group, the physical component score improved from 32.9 ± 10.0 at baseline to 35.9 ± 9.4 at 30 days, and the mental component scores were 47.2 ± 11.1 at baseline and 47.2 ± 14.0 at 30 days.

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

PIIS3HR pivotal clinical study involved 196 investigators of which none were full-time or part-time employees of the sponsor including six (6) investigators that 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: 6 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.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The supplemental clinical data to the PMA application came from a study (referred to as "S3OUS" hereafter) conducted in Europe and Canada to support the CE Mark.

A. Study Design

The S3OUS study was a non-randomized, prospective, multi-center study in inoperable, high surgical risk, and intermediate surgical risk patients who underwent implantation of the 23, 26, or 29 mm SAPIEN 3 THV.

Except the intermediate surgical risk patients, the inclusion/exclusion criteria of the S3OUS trial were largely similar to those of the PIIS3HR trial. However, the S3OUS study had a minimum age requirement ($\geq$ 75 years) and the upper limit for AVA was higher (< 1 cm^2 instead of ≤ 0.80 cm^2). Additionally, the S3OUS study allowed for the inclusion of patients with the following: BAV within 30 days of the procedure (unless BAV was a bridge to procedure); planned concomitant surgical or transcatheter ablation for atrial fibrillation; hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of screening; and the need for emergency surgery for any reason. Furthermore, the exclusion criteria in the S3OUS study excluded senile dementia and any neurologic disease which severely affected the ability to walk or perform everyday activities, and shortened the time interval regarding confirmed stroke or TIA (within 3 months instead of 6 month of the procedure). The follow-up periods were discharge or 7 days, whichever comes first, 30 days, 1 year, and annually thereafter to a minimum of 5 years post procedure.

B. Accountability of the S3OUS Cohort

Patients were treated between January 3, 2013 and October 23, 2013 at 14 investigational sites. Note that the intermediate risk patients enrolled in the S3OUS study were excluded from the analysis presented herein. The database reflects data collected through November 19, 2014 and included 102 "all treated" (AT) inoperable and high surgical risk patients. "All treated" population is defined to include all patients who were enrolled in the trial and for whom the study valve implantation procedures were started (i.e., the anesthesia was started).

One patient was excluded from the VI population. This patient experienced an aortic root rupture caused by displacement of a large lump of calcium with sharp edges through the native aortic annulus following balloon expansion of the SAPIEN 3 THV. The patient was subsequently converted to SAVR. After the patient was weaned of cardio-pulmonary bypass, bleeding in the region of the dorsal root occurred, and the patient died on the operating table.

A total of 56 patients were successfully implanted with a SAPIEN 3 THV via the transfemoral access route, and 45 via the transapical/transaortic access route, as shown in Table 20. At the time of database lock, 80 of the 102 AT patients were still alive and had not withdrawn consent, and all had completed the 1-year post-operative visit.

Table 20: Patient Accountability (S3OUS)

Overall		TF		TA/TAo	
All Treated (AT) Population	**Valve Implant (VI) Population**	**All Treated (AT) Population**	**Valve Implant (VI) Population**	**All Treated (AT) Population**	**Valve Implant (VI) Population**
102	101	57	56	45	45
All Treated (AT) Population consists of all patients who were enrolled in the trial and for whom the study valve implantation procedures were started (i.e., the anesthesia was started). Valve Implant (VI) Population consists of all enrolled patients who received a SAPIEN 3 implant, and retained the valve upon leaving the catheterization laboratory/hybrid suite.					

C. Study Population Demographics and Baseline Parameters

The demographics of the S3OUS study population are shown in Table 21.

Table 21: Patient Demographics and Baseline Characteristics (S3OUS AT Population)

Demographics and Baseline Characteristics	Overall (N= 102)	TF (N= 57)	TA/TAo (N= 45)
Age, yr	84.1 ± 5.0	85.1 ± 4.6	83.0 ± 5.3
Male sex, no.(%)	40 (39.2%)	23 (40.4%)	17 (37.8%)
STS score	8.0 ± 4.7	8.2 ± 4.2	7.9 ± 5.2
Logistic EuroSCORE	24.1 ± 13.0	22.3 ± 11.3	26.4 ± 14.7
New York Heart Association (NYHA) class, no.(%):			
I/II	11 (10.8%)	6 (10.5%)	5 (11.1%)

Demographics and Baseline Characteristics	Overall (N= 102)	TF (N= 57)	TA/TAo (N= 45)
III/IV	91 (89.2%)	51 (89.5%)	40 (88.9%)
Coronary artery disease, no.(%)	68 (66.7%)	36 (63.2%)	32 (71.1%)
Previous myocardial infarction, no.(%)	20 (19.6%)	7 (12.3%)	13 (28.9%)
Previous intervention, no.(%)			
Coronary-artery bypass grafting (CABG)	24 (23.5%)	10 (17.5%)	14 (31.1%)
Percutaneous coronary intervention (PCI)	34 (33.3%)	16 (28.1%)	18 (40.0%)
Prior aortic valvuloplasty	10 (9.8%)	8 (14.0%)	2 (4.4%)
Stroke, no.(%)	7 (6.9%)	4 (7.0%)	3 (6.7%)
Peripheral vascular disease, no.(%)	27 (26.5%)	10 (17.5%)	17 (37.8%)
Chronic obstructive pulmonary disease (COPD), no.(%):			
Any	25 (24.5%)	13 (22.8%)	12 (26.7%)
Oxygen-dependent	1 (1.0%)	1 (1.8%)	0 (0%)
Atrial fibrillation, no.(%)	48 (47.1%)	22 (38.6%)	26 (57.8%)
Permanent pacemaker, no.(%)	15 (14.7%)	7 (12.3%)	8 (17.8%)
Severe pulmonary hypertension, no.(%)	10 (9.8%)	6 (10.5%)	4 (8.9%)
Severe liver disease / Cirrhosis, no.(%)	1 (1.0%)	1 (1.8%)	0 (0%)
Echocardiographic findings			
Effective Orifice Area (EOA), cm^2	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.1
Mean aortic-valve gradient, mmHg	44.8 ± 15.3	45.2 ± 14.7	44.2 ± 16.1
Mean left ventricular ejection fraction (LVEF), %	56.7 ± 9.1	57.7 ± 9.3	55.3 ± 8.7
Moderate or severe mitral regurgitation, no./total no. (%)	23/85 (27.1%)	9/48 (18.8%)	14/37 (37.8%)

Plus–minus values are means ± SD.

D. Safety and Effectiveness Results

Key Adverse Events

Key adverse events as adjudicated by the CEC are presented in Table 22.

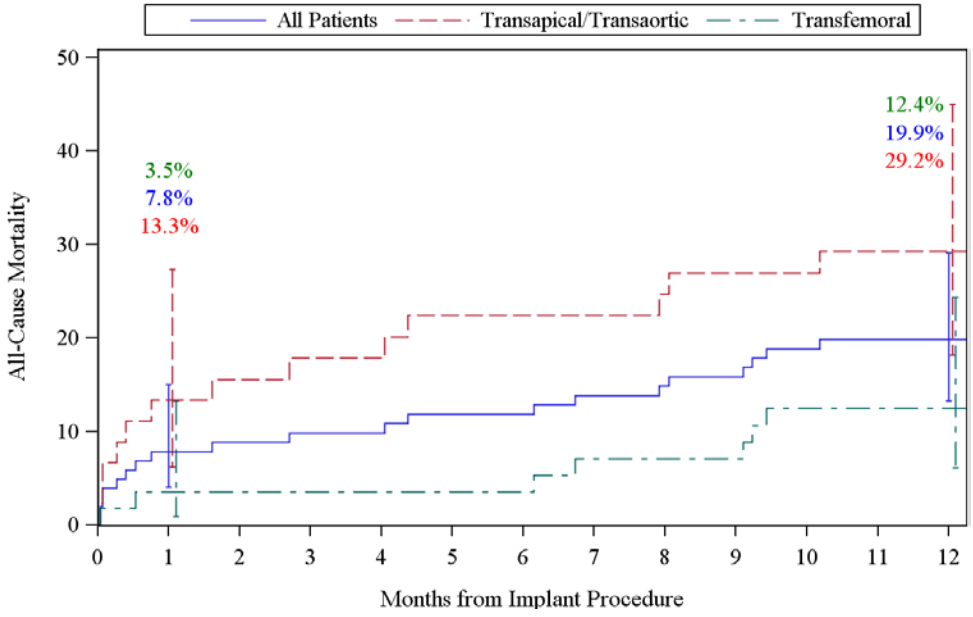
Table 22: CEC Adjudicated Adverse Events at 1 Year (S3OUS AT Population)

	30 Day			1 Year		
Outcomes	**Overall**	**TF**	**TA/TAo**	**Overall**	**TF**	**TA/TAo**
Composite Event Rate of Death, All Stroke and AI ≥ Moderate, n/N (%)	13/88 (14.8%)	3/50 (6.0%)	10/38 (26.3%)	25/82 (30.5%)	9/47 (19.1%)	16/35 (45.7%)
Death						
From Any Death, n/N (%)	8/102 (7.8%)	2/57 (3.5%)	6/45 (13.3%)	20/102 (19.6%)	7/57 (12.3%)	13/45 (28.9%)
From cardiovascular cause, n/N (%)	7/102 (6.9%)	2/57 (3.5%)	5/45 (11.1%)	9/102 (8.8%)	2/57 (3.5%)	7/45 (15.6%)
Stroke, n/N (%)	3/102 (2.9%)	1/57 (1.8%)	2/45 (4.4%)	5/102 (4.9%)	2/57 (3.5%)	3/45 (6.7%)
Aortic Insufficiency (AI) ≥ Moderate, n/N (%)	3/81 (3.7%)	1/49 (2.0%)	2/32 (6.3%)	1/62 (1.6%)	1/40 (2.5%)	0/22 (0.0%)

	30 Day			1 Year		
Outcomes	**Overall**	**TF**	**TA/TAo**	**Overall**	**TF**	**TA/TAo**
Disabling Stroke, n/N (%)	0/102 (0.0%)	0/57 (0.0%)	0/45 (0.0%)	1/102 (1.0%)	1/57 (1.8%)	0/45 (0.0%)
Myocardial Infarction, n/N (%)	2/102 (2.0%)	2/57 (3.5%)	0/45 (0.0%)	3/102 (2.9%)	2/57 (3.5%)	1/45 (2.2%)
Major Vascular Complications, n/N (%)	5/102 (4.9%)	1/57 (1.8%)	4/45 (8.9%)	N/A	N/A	N/A
Acute Kidney Injury - Stage III, n/N (%)	0/102 (0.0%)	0/57 (0.0%)	0/45 (0.0%)	N/A	N/A	N/A
Disabling Bleeding Event, n/N (%)	6/102 (5.9%)	3/57 (5.3%)	3/45 (6.7%)	N/A	N/A	N/A
THV Dysfunction Requiring Intervention, n/N (%)	0/102 (0.0%)	0/57 (0.0%)	0/45 (0.0%)	N/A	N/A	N/A
Prosthetic Valve Endocarditis, n/N (%)	0/102 (0.0%)	0/57 (0.0%)	0/45 (0.0%)	1/102 (1.0%)	0/57 (0.0%)	1/45 (2.2%)
Conduction Abnormality Requiring Pacemaker, n/N (%)	14/102 (13.7%)	7/57 (12.3%)	7/45 (15.6%)	14/102 (13.7%)	7/57 (12.3%)	7/45 (15.6%)

The K-M estimates for all-cause mortality for all patients, the TF patients, and the TA/TAo patients are shown in Figure 14.

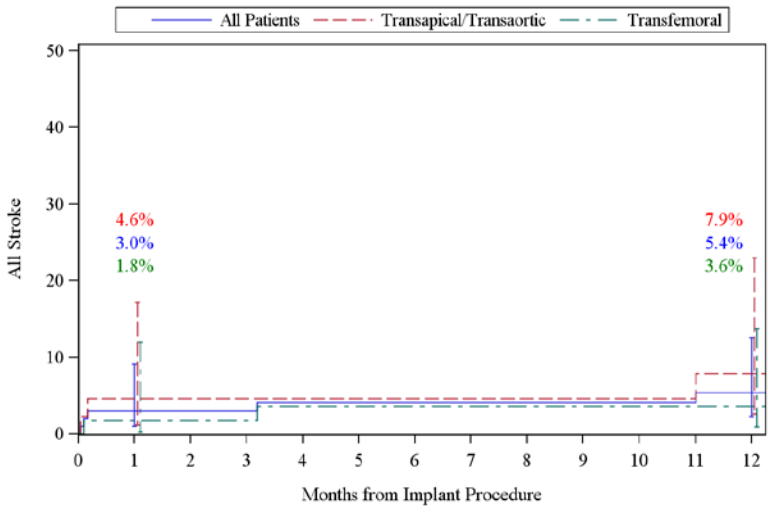
Figure 14: All-Cause Mortality at 1 Year (S3OUS AT Population)



Note: The confidence intervals are calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

The K-M estimates for the stroke rate for all patients, the TF patients, and the TA/TAo patients are shown in Figure 15.

Figure 15: All Stroke at 1 Year (S3OUS AT Population)

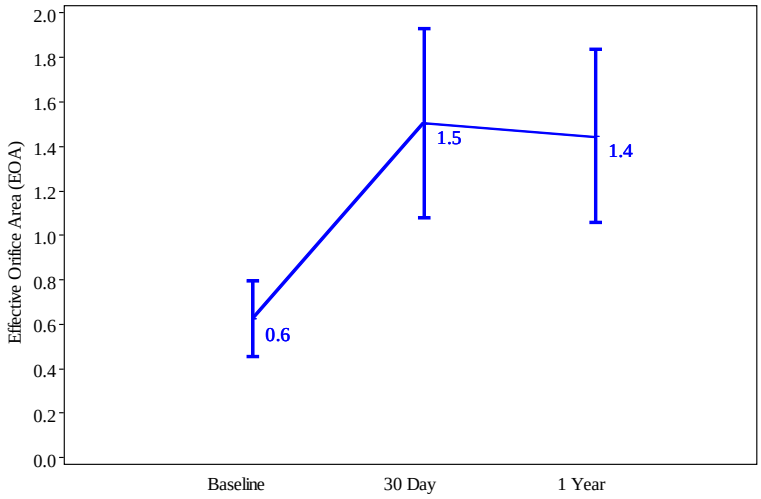


Note: The confidence intervals are calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Valve Performance

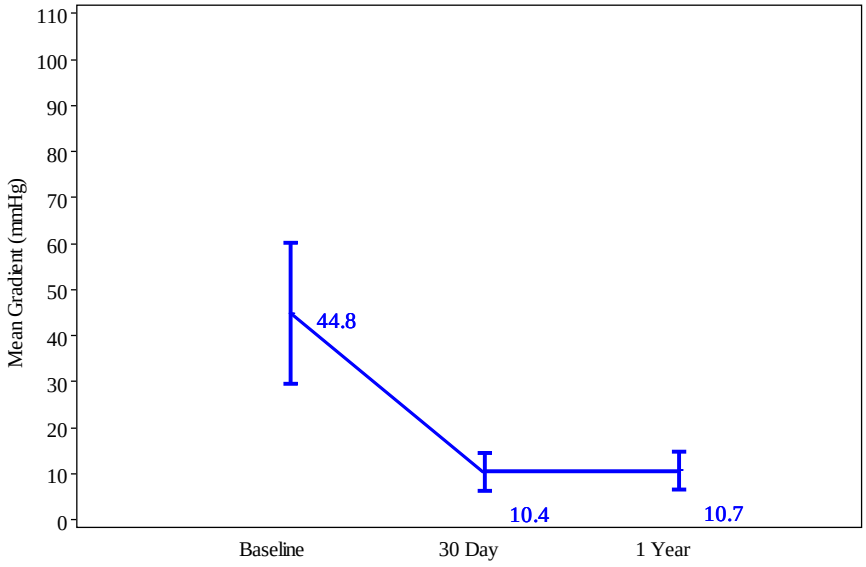
The mean EOA increased from 0.6 ± 0.2 cm^2 at baseline to 1.5 ± 0.4 cm^2 at 30 days and 1.4 ± 0.4 cm^2 at 1 year, as shown in Figure 16.

Figure 16: Effective Orifice Area (S3OUS VI Population)



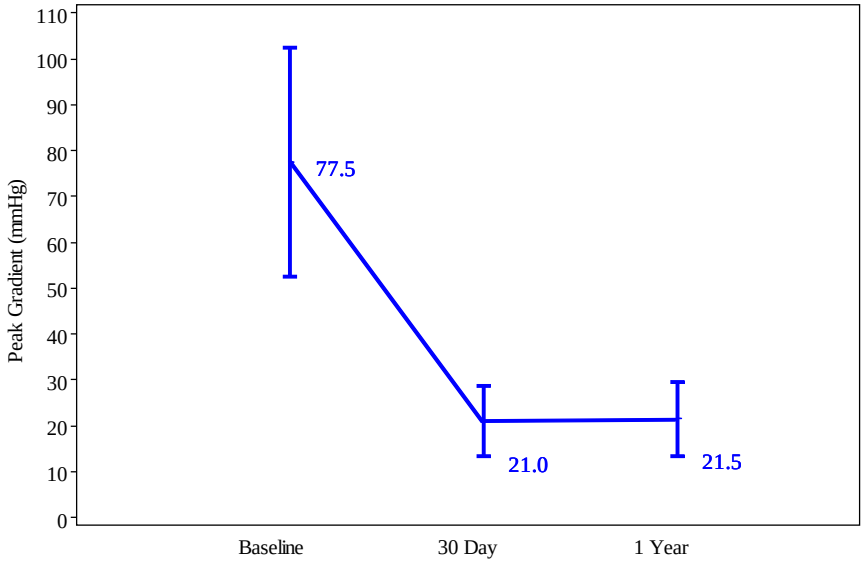
The average mean gradient decreased from 44.8 ± 15.4 mmHg at baseline to 10.4 ± 4.1 mmHg at 30 days and maintained at 10.7 ± 4.1 mmHg at 1 year, as shown in Figure 17.

Figure 17: Mean Gradient (S3OUS VI Population)



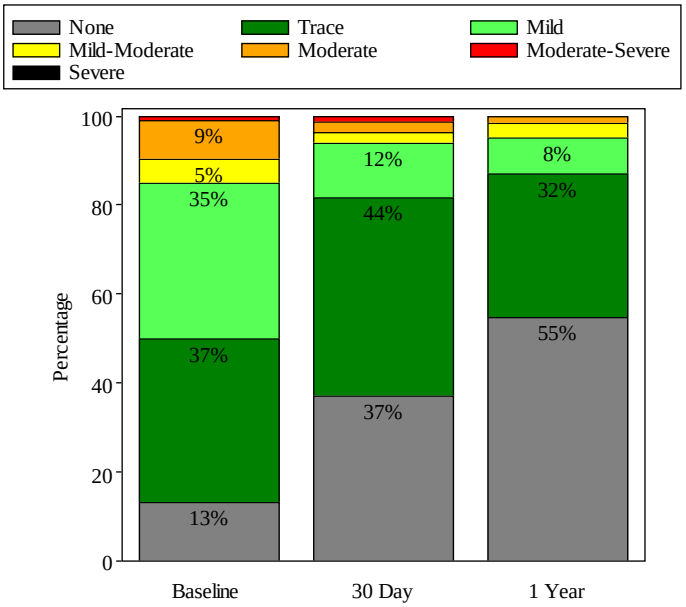
The mean peak gradient decreased from 77.5 ± 24.9 mmHg at baseline to 21.0 ± 7.7 mmHg at 30 days, and maintained at 21.5 ± 8.2 mmHg at 1 year, as shown in Figure 18.

Figure 18: Peak Gradient (S3OUS VI Population)



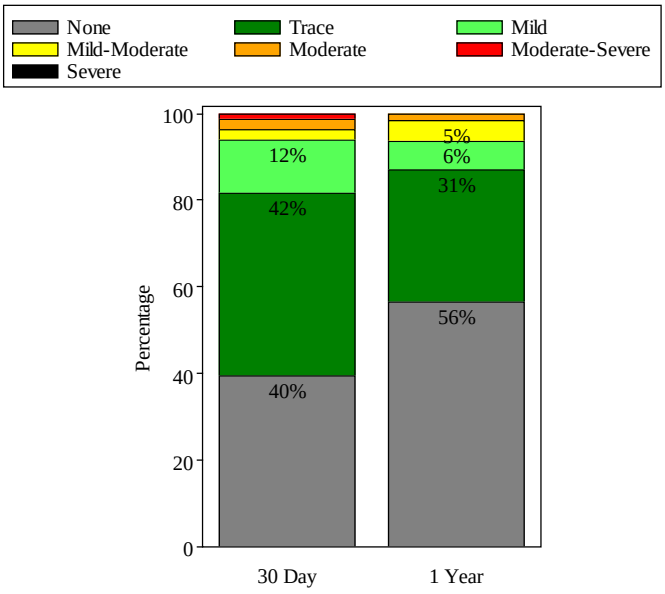
The proportion of patients with aortic insufficiency ≥ moderate was 9.8% at baseline, 3.7% at 30 days, and 1.6% at 1 year, as shown in Figure 19.

Figure 19: Aortic Insufficiency (S3OUS VI Population)



The proportion of patients with aortic PVL ≥ moderate was 3.7% at 30 days, and 1.6% at 1 year, as shown in Figure 20.

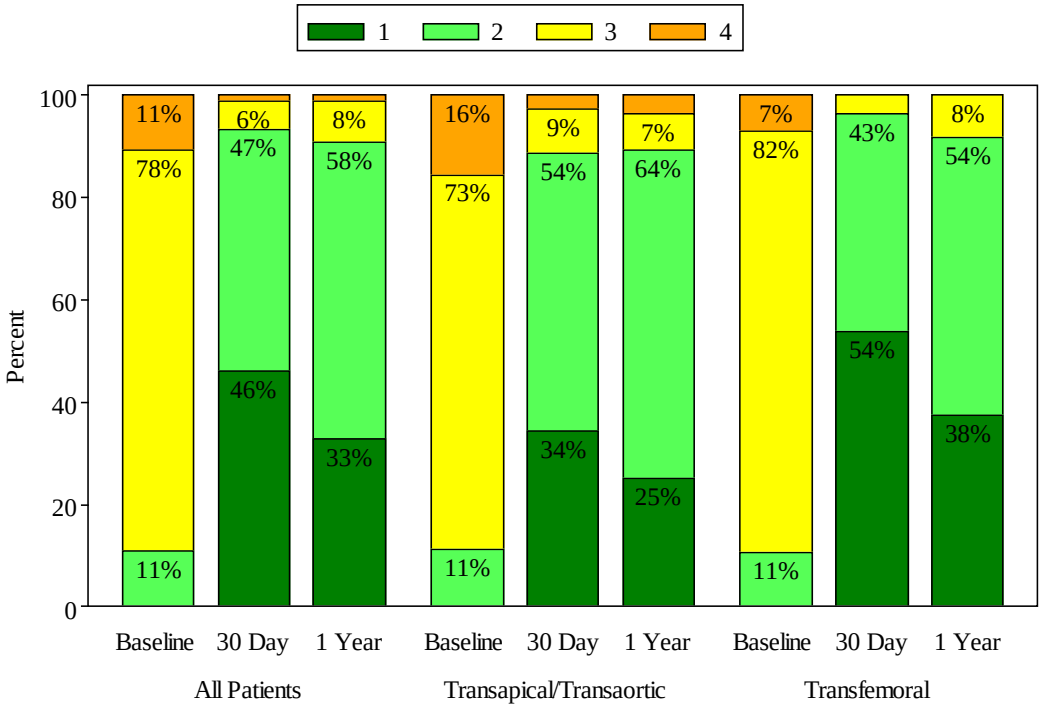
Figure 20: Aortic Paravalvular Leak (S3OUS VI Population)



NYHA

The NYHA class by visit is shown in Figure 21. For all patients, the mean NYHA class decreased from 3.0 ± 0.5 at baseline to 1.6 ± 0.7 at 30 days and 1.8 ± 0.6 at 1 year.

Figure 21: NYHA Class by Visit (S3OUS AT Population)



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

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

XIII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The results from the preclinical studies performed on the Edwards SAPIEN 3 THV for biocompatibility, hydrodynamic performance, durability, and structural integrity demonstrate that this device is suitable for long-term implant.

The composite event rate of all-cause mortality, all stroke, and AI ≥ moderate at 30 days (i.e., the primary endpoint) was 6.7% in the SAPIEN 3 cohort (test arm) and 15.6% in the SAPIEN cohort (historical control arm). The upper limit of the 90% confidence interval of the proportion difference in the primary endpoint using the ATT method was -0.5%, which was lower than the pre-specified non-inferiority margin of 7.5%. As such, the pivotal clinical study met the pre-specified primary endpoint. The K-M estimated rates of all-cause mortality (2.2%) and all stroke (1.6%) were numerically lower in the SAPIEN 3 cohort as compared to those (4.6% and 4.3%, respectively) in the SAPIEN cohort.

The proportion of patients with AI ≥ moderate at 30 days was 3.0% for the SAPIEN 3 cohort and 14.3% for the SAPIEN cohort (p=0.0051), which demonstrated that the SAPIEN 3 THV was superior to SAPIEN THV in this secondary endpoint. The estimated event rate of major vascular complications at 30 days was 5.0% for the SAPIEN 3 cohort and 10.1% for the SAPIEN cohort (p=0.0578), which indicated that the SAPIEN 3 THV was not statistically different from SAPIEN THV in major vascular complications.

Of note is that the rate of conduction disturbance requiring permanent pacemaker following implantation of the SAPIEN 3 THV (13.0%) was much higher than that for the SAPIEN THV as observed in previous U.S. pivotal trials, which ranged from 3.4% to 5.9%.

B. ***Effectiveness Conclusions***

In the clinical study, the subjects overall demonstrated significant improvement in valve hemodynamics from baseline to 30 days. On average, the EOA increased from 0.7 cm^2 to 1.6 cm^2, the mean pressure gradient decreased from 45.5 mmHg to 11.1 mmHg, and the peak pressure gradient decreased from 75.8 mmHg to 21.2 mmHg.

The improvement in valve hemodynamics is further demonstrated through improvements in NYHA classification and QoL measures. About 87% of subjects were in NYHA I/II at 30 days as compared to 10% at baseline. The mean VAS of the EuroQoL (EQ-5D) measure and overall KCCQ score increased by 14.6 and 20.6, respectively, from baseline to 30 days.

C. ***Benefit-Risk Conclusions***

The probable benefits of the SAPIEN 3 THV are based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefits include improved valve hemodynamic performance, improved functional status as measured by NYHA classification, and improved QoL at 30 days, as compared to baseline.

The probable risks of the SAPIEN 3 THV include procedure related complications such as death, stroke, myocardial infarction, major vascular complications, bleeding, conduction disturbance, and acute kidney injury.

The overall benefit/risk profile of the SAPIEN 3 THV is similar to that of the SAPIEN THV. In particular, the SAPIEN 3 THV will have significantly less AI ≥ moderate at 30 days.

In conclusion, given the available information above, the data support that for patients with severe native aortic stenosis who are at high or greater risk for open aortic valve replacement surgery, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The preclinical and clinical studies submitted in the PMA application provide reasonable assurance that the SAPIEN 3 THV, available in valve sizes 20, 23, 26, and 29 mm, is safe and effective for the replacement of native aortic valves in symptomatic severe aortic stenosis patients who are deemed to be at high or greater surgical risk, defined as having an STS operative risk score ≥8% or a ≥15% risk of mortality at 30 days.

XIV. CDRH DECISION

CDRH issued an approval order on June 17, 2015. The final conditions of approval cited in the approval order are described below.

The applicant must conduct one post-approval study as well as participate in and support one surveillance study:

1. ***ODE Lead Post-Approval Study (Continued follow-up of the premarket cohort)***: The study will consist of all living subjects who were enrolled under the IDE in the PIIS3HR Cohort and NR7. The objective of this study is to characterize the clinical outcomes annually through 5 years post-procedure. The safety and effectiveness endpoints include all-cause mortality, all stroke, total days alive and out of hospital (from date of index procedure), improvement per New York Heart Association (NYHA) Class (from baseline), improvement in 6 Minute Walk Test (at one year only), improvement per Kansas City Cardiomyopathy Questionnaire (KCCQ) and Euro Health Related Quality of Life (EQ5D), valve performance, major vascular complications, myocardial infarction, new permanent pacemaker, new onset atrial fibrillation, and bleeding.

2. ***OSB Lead 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 3 device over the next 5 years. This surveillance will 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, acute events associated with index TAVR procedure), peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months; (3) neurological (non-stroke), vascular complications, and quality of life

(KCCQ) outcomes at 30 days and 12 months; and (4) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) annually through 5 year post implantation.

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

XV. APPROVAL SPECIFICATIONS

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

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

Post-approval Requirements and Restrictions: See Approval Order.

XVI. REFERENCES

[1] Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). Eur J Cardiothorac Surg 2012;42:S45-60.

[2] Imbens GW. Nonparametric Estimation of Average Treatment Effects under Exogeneity: A Review. Rev Econ Statist 2004; 86: 4-29.