

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic

Name: Pulmonic 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; Edwards crimper, model 9350CR)

Device Procode: NPV

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

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P130009/S037

Date of FDA Notice of Approval: February 29, 2016

The original PMA (P130009) was approved on June 16, 2014 and is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area $\leq 1.0 \text{ cm}^2$ or aortic valve area index $\leq 0.6 \text{ cm}^2/\text{m}^2$, a mean aortic valve gradient of $\geq 40 \text{ mmHg}$, or a peak aortic-jet velocity of $\geq 4.0 \text{ m/s}$), 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). The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Edwards SAPIEN XT Transcatheter Heart Valve to include pulmonic implantation.

II. INDICATIONS FOR USE

The Edwards SAPIEN XT Transcatheter Heart Valve (THV) Systems are indicated for use in pediatric and adult patients with a dysfunctional, non-compliant Right Ventricular Outflow Tract (RVOT) conduit with a clinical indication for intervention and:

- pulmonary regurgitation \geq moderate and/or
- mean RVOT gradient \geq 35 mmHg.

III. CONTRAINDICATIONS

The SAPIEN XT and delivery systems are contraindicated in patients with

- Inability to tolerate an anticoagulation/antiplatelet regimen
- Active bacterial endocarditis

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the SAPIEN XT labeling.

V. DEVICE DESCRIPTION

The Edwards SAPIEN XT THV (**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.

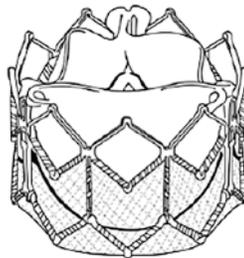


Figure 1: SAPIEN XT Transcatheter Heart Valve

The NovaFlex+ delivery system (**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 tracking to the target location, a balloon catheter for deployment of the THV, and radiopaque markers.

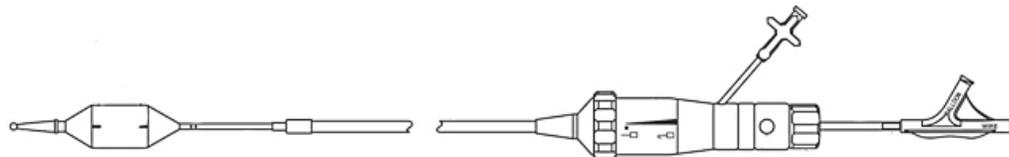


Figure 2: NovaFlex+ Delivery System

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

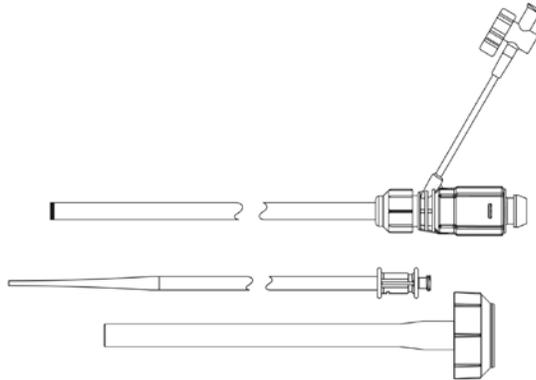


Figure 3: Edwards Expandable Introducer Sheath Set

The Qualcrimp crimping accessory (**Figure 4**) 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. It is manufactured of tubular polyester polyurethane foam that is laminated cylindrically on both the inner and outer surfaces with a polyether urethane material.

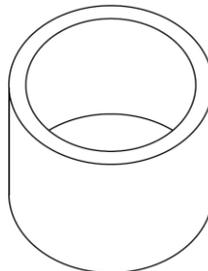


Figure 4: Qualcrimp Crimping Accessory

The Edwards crimper (**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 includes a 2-piece crimp stopper (packaged with the NovaFlex+ delivery system) used to correctly crimp the THV.

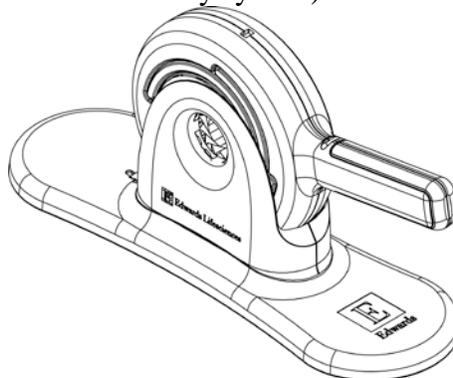


Figure 5: Edwards Crimper

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of dysfunctional non-compliant RVOT conduits. These alternatives include balloon angioplasty, surgical replacement of the RVOT conduit with either a homograft or conduit with an integral bioprosthetic valve and replacement using an approved transcatheter heart valve. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Pulmonic SAPIEN XT THV and accessories may be commercially distributed under the European Union: Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the UK.

The SAPIEN XT THV has not been withdrawn from market for any reason related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Death
- 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 Arrhythmia
- Arteriovenous fistula
- Reoperation or reintervention
- Ischemia or nerve injury
- 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 or ecchymosis
- Syncope
- Pain or changes at the access site
- Exercise intolerance or weakness
- Inflammation
- Angina
- Fever

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

- Cardiac arrest
- Cardiogenic shock
- Emergency cardiac surgery
- Coronary flow obstruction/transvalvular flow disturbance
- Device thrombosis requiring intervention
- Valve thrombosis
- Device embolization
- Device malposition requiring intervention
- Valve deployment in unintended location
- 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)
- Paravalvular or transvalvular leak
- Valve regurgitation
- Hemolysis
- Device explants
- Nonstructural dysfunction
- Mechanical failure of delivery system, and/or accessories

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

IX. SUMMARY OF PRECLINICAL 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 ISO 5840-3(2013): *Cardiovascular Implants-Cardiac Valve Prostheses Part 3: Heart valve substitutes* implanted by transcatheter techniques.

The SAPIEN XT THV was evaluated under the same preclinical tests and acceptance criteria as the SAPIEN THV. Testing was referenced from PMA submission P130009 for those evaluations that could be leveraged from aortic testing. A summary of previously

reported preclinical studies can be found in the Summary of Safety and Effectiveness Data (SSED) for the original PMA

(http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130009b.pdf).

Additional testing performed to support the specific pulmonic conditions is presented below.

A. Laboratory Studies

1. SAPIEN XT THV Hydrodynamic Performance

In vitro hydrodynamic performance studies of the SAPIEN XT bioprosthesis 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 ISO 5840-3(2013): *Cardiovascular Implants-Cardiac Valve Prostheses Part 3: Heart valve substitutes implanted by transcatheter techniques*. Testing included pressures at pulmonic conditions as indicated in ISO 5840-3(2013).

Table 1: Hydrodynamic Testing and Results

Test	Purpose	Test/Reference Articles	Results
Pulsatile pressure drop and effective orifice area (EOA)	To determine pressure drop and effective orifice area performance under pulsatile flow conditions.	<p><u>Nominal Configuration Valves</u> Test: Size 23: SAPIEN XT Size 26: SAPIEN XT Size 29: SAPIEN XT</p> <p>Reference: Size 23: SAPIEN, Perimount Magna Size 26: SAPIEN, Perimount Magna Size 29: Perimount Magna</p> <p><u>Irregular Configuration Valves</u> Test: Size 23: SAPIEN XT Size 26: SAPIEN XT Size 29: SAPIEN XT</p> <p>Reference: Size 23: Nominal SAPIEN and SAPIEN XT Size 26: Nominal SAPIEN and SAPIEN XT Size 29: Nominal SAPIEN XT</p>	<p>The SAPIEN XT valves demonstrated acceptable hydrodynamics (EOA, pressure gradient, and regurgitation) with respect to that required by the ISO 5840-3:2013 acceptance criteria when tested under pulmonic conditions.</p> <p>Effective Orifice Area (EOA) of the SAPIEN XT valves were evaluated at a variety of aortic pulsatile conditions and demonstrated comparable results between SAPIEN XT and reference valves. Test Condition 2 of mean leakage pressures of 10 ± 5 mmHg at 5 liters per minute and 70 beats per minute is utilized to analyze EOA and leakage values for pulmonic conditions. All EOA and regurgitation results exceeded the minimum device performance requirements from ISO 5840-3:2013, Table 3.</p> <p>These results indicate that the SAPIEN XT meets the EOA hydrodynamic and transvalvular regurgitant fraction hydrodynamic performance requirements under pulmonic conditions.</p>

2. SAPIEN XT THV DURABILITY TESTING

In vitro durability assessment for the SAPIEN XT THV was performed under pulmonic conditions. The studies were conducted in accordance with ISO 5840: *Cardiovascular Implants-Cardiac Valve Prostheses* (2013). Testing was performed at pulmonic pressures as indicated in ISO 5840: *Cardiovascular Implants-Cardiac Valve Prostheses* (2013). Commercially available SAPIEN XT valves under aortic conditions were used as the reference articles.

Table 2: Structural Performance Evaluation

Test	Purpose/Objective	Test/Reference Articles	Results
Durability assessment Accelerated Wear	To assess long-term performance of the valve though accelerated wear.	<u>Pulmonic Position (Test Articles):</u> <ul style="list-style-type: none"> • n = 9 test articles SAPIEN XT (model 9300TFX, 3 size 23mm, 3 size 26mm, and 3 size 29mm), maximum sterilization, maximum BReP, Glutaraldehyde TLS, shipping simulation, nominal deployment <u>Aortic Position (Reference Articles):</u> <ul style="list-style-type: none"> • n = 3 reference articles SAPIEN XT (model 9300TFX, 1 size 23mm, 1 size 26mm, and 1 size 29mm), sterile, nominal deployment • n = 3 reference articles Magna Ease surgical valve (model 3300TFX, 1 size 23mm, 1 size 27mm, and 1 size 29mm), sterile 	<p>PASS</p> <p>The test valves remained functional without structural damage through 200 million cycles and met the requirements of ISO 5840-3:2013 for EOA and regurgitant fraction.</p> <p>No visual signs of functional impairment of the valves were observed at the completion of 200 million cycles.</p>

B. Animal Studies

1. Crimping and Implantation

Animal testing was conducted under pulmonic conditions to evaluate valve crimping and implantation in the antegrade orientation in order to simulate pulmonic procedures.

Table 3: Animal Calcification Study

Test	Purpose/Objective	Test/Reference Articles	Results
Antegrade crimping and deployment	To assess the effect of antegrade crimping and deployment on tissue calcification	<p>N=33 New Zealand White Rabbits were implanted with eight tissue discs from control and test articles</p> <p><u>Test articles</u></p> <ul style="list-style-type: none"> • 23 and 29mm SAPIEN XT THV crimped and implanted in antegrade direction <p><u>Control articles</u></p> <ul style="list-style-type: none"> • 29mm SAPIEN XT THV crimped and implanted in the retrograde direction • Glutaraldehyde only treated tissue 	<p>PASS</p> <p>Histology and calcium analysis was performed. The test and control articles were observed to be equivalent.</p>

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of pulmonic implantation with the Edwards SAPIEN THV in patients with dysfunctional RVOT conduits in the US under IDE # G060242 (entitled the **C**ongenital **M**ulticenter trial of **P**ulmonic v**A**lve regurgitation **S**tudying the **S**APIEN Intervent**I**ONal THV, “COMPASSION” trial). Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between April 17, 2008 and November 24, 2014. The database for this Panel Track Supplement reflected data collected through March 6, 2015 and included 81 patients. There were 7 investigational sites.

The study was a prospective, non-randomized, multi-center clinical study to assess the safety and effectiveness of pulmonic implantation of the SAPIEN THV in patients with dysfunctional RVOT conduits requiring treatment for moderate or severe pulmonary regurgitation (PR) by transthoracic echocardiography (TTE) and/or RVOT conduit obstruction with a mean gradient of ≥ 35 mmHg by TTE. The SAPIEN THV is the first generation valve of the SAPIEN device line and is no longer available for distribution. The valve sizes used in the COMPASSION trial included the 23 and 26 mm sizes which were the only available sizes for the SAPIEN THV. The 29 mm valve size was not evaluated in the COMPASSION trial and therefore data for this device size is unavailable. The majority of data were derived from patients who received the 23mm THV size. Aortic experience with the 29 mm SAPIEN XT THV showed no significant difference in long term performance in comparison to the 23 mm and 26 mm SAPIEN XT THV sizes. Furthermore, no observed results suggest that the 29 mm valve size would perform worse than other available sizes in the pulmonic location.

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 definitions established *a priori*, an Echocardiographic (ECG) Core Lab for independent analysis all echocardiograms, and a Cardiac Magnetic Resonance Imaging (MRI) Core Lab for independent analysis of all cardiac MRI data.

1. Clinical Inclusion and Exclusion Criteria

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

- Weight \geq 35 kilograms.
- *In situ* conduit size of 20-26 mm in diameter (per Instructions for Use).
- Moderate or severe pulmonary regurgitation defined as \geq 3+ PR by TTE **or** RVOT conduit obstruction with a mean gradient of \geq 35 mmHg by TTE.
- Symptomatic as evidenced by cardiopulmonary exercise testing.
- The patient or the 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 patient and the treating physician agreed that the patient would return for all required post-procedure follow-up visits and the patient would comply with protocol-required follow-up visits.
- Catheterization was determined to be feasible by the treating physician.

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

- Active infection requiring current antibiotic therapy. (If temporary illness, the patient could qualify for study participation 4 weeks after discontinuation of antibiotics.)
- Previously enrolled in this study.
- Pre-existing prosthetic heart valves in any position.
- Severe chest wall deformity.
- Leukopenia (WBC < 3000 cells/mm³).
- Acute or chronic anemia (Hb < 9 g/dL).
- Platelet count < 100,000 cells/mm³.
- In the judgment of the Investigator, percutaneous introduction and delivery of the SAPIEN THV device was not feasible.
- Need for emergency cardiac or vascular surgery, including pulmonary embolectomy, for any reason.
- Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
- History of endocarditis (i.e., within the past 6 months), or active endocarditis.
- History of intravenous drug abuse, or current intravenous drug abuse.
- Known hypersensitivity to aspirin or heparin.
- Currently participating in an investigational drug or another device study.

- Major or progressive non-cardiac disease resulting in a life expectancy of < 1 year.
- Obstruction of the central veins preventing advancement of the pulmonic bioprosthesis delivery system to the heart.
- Positive urine or serum pregnancy test in female patients of child-bearing potential.
- Right ventricular outflow tract aneurysm.
- Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath.
- Need for concomitant interventional procedures such as ASD (atrial septal defect) or VSD (ventricular septal defect) closure.
- Previous angiographic evidence of coronary artery compression.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at day 1 post-procedure, discharge, 30 days, 6 months, 12 months, and annually thereafter for 5 years postoperatively. The follow-up schedule included the following:

Baseline:

- TTE, X-ray, MRI or CT, angiogram, ECG

Immediate Post-procedure and discharge

- TTE, X-ray, ECG

30 Days and 6 months

- TTE, X-ray, ECG, and NYHA class

6 Months

- TTE, X-ray, MRI or CT, angiogram, ECG, and NYHA class

Annually up to 5 years

- TTE, X-ray, angiogram, ECG, and NYHA class

Adverse events and complications were recorded at all visits.

The key time points are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

The primary endpoint was freedom from device- or procedure-related death and/or reintervention at 1 year.

The secondary endpoints were as follows:

- 1) Freedom from Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 6 months. MACCE was defined as all-cause mortality, myocardial infarction, reintervention, vascular injury resulting in the need for an unplanned vascular intervention, stroke and pulmonary embolism.
- 2) Functional improvement at 6 months as defined by:
 - a. Improved valve hemodynamics as demonstrated via TTE:

- i. Decrease in pulmonary regurgitation to mild or less for regurgitant lesions
- ii. Decrease in mean pulmonary gradient to less than 30mmHg for stenotic lesions
- iii. Improvement in both i) and ii) above for mixed lesions.
- b. Improvement of ≥ 1 NYHA functional class from baseline for patients with NYHA functional class ≥ 2 at baseline.
- c. Freedom from recurrent pulmonary stenosis.

B. Accountability of PMA Cohort

At the time of database lock, of 81 patients enrolled in the PMA study (**Table 4**). Two enrolled patients were screen failures and did not undergo the index procedure; therefore, there were 79 patients in the safety population. A device was not used nor inserted into the vascular system in 9 patients in the safety population; therefore, there were 70 patients in the attempted implant population. One patient did not have a SAPIEN THV implanted in the target location; therefore, there were 69 patients available for analysis in the valve implant population at the completion of the study. The total study follow-up time for the safety population is shown in **Table 5**.

Table 4: Patient Accountability (All Enrolled Patients)

	Enrolled	Safety Population [1]	Attempted Implant Population [2]	Valve Implant Population [3]
COMPASSION	81	79	70	69

[1] Safety Population: All enrolled subjects for whom the procedure has begun, regardless of whether the valve was successfully implanted. The definition of “procedure has begun” is “the time of the creation of vascular access - incision or puncture.”

[2] Attempted Implant Population: A participant is considered to have an attempted implant if they either:

- a) Have the study valve implanted in the target location, or
- b) A study valve was inserted (defined by the use of the study valve), but the valve was not implanted or retained after the procedure, or implanted outside of the target location.

[3] Valve-Implant Population: All enrolled patients who have the study valve implanted in the target location. The valve implanted population is the population used for analysis.

Table 5. Total Study Follow-up Time in the Safety Population (N=79)

Summary Statistic	Results
Total Follow-up Time (years)	2.78±1.74 (79) 3.04 (0.00, 5.31)
Total Patient Years [1]	219.8

Summary statistics:

Continuous measures- Mean ± SD (N); Median (Min, Max)

[1] Total patient years is the sum of the time on study for all patients

C. Study Population Demographics and Baseline Parameters

The demographics and baseline characteristics of the safety population are summarized in **Table 6**.

Table 6: Demographics and Baseline Characteristics (Safety Population)

Characteristic	Statistic
Age - yr	28.0 ± 13.97 (79)
	25.0 (10.0, 72.0)
<12 Years(Child)	3 / 79 (3.8%)
12-21 Years (Adolescent)	26 / 79 (32.9%)
>=22 Years (Adult)	50 / 79 (63.3%)
Male sex	52 / 79 (65.8%)
NYHA class	
I	18 / 79 (22.8%)
II	36 / 79 (45.6%)
III	23 / 79 (29.1%)
IV	2 / 79 (2.5%)
Primary Indication	
Pulmonary Stenosis	7 / 79 (8.9%)
Pulmonary Regurgitation	10 / 79 (12.7%)
Both	62 / 79 (78.5%)
Any Stent Placed (Prior to Study or During Study Procedure)	71 / 78 (91.0%)
Valve size (mm)	
23	48 / 70 (68.6%)
26	22 / 70 (31.4%)
Pulmonary Stenosis	
None	10 / 79 (12.7%)
Mild	13 / 79 (16.5%)
Moderate	25 / 79 (31.6%)
Severe	31 / 79 (39.2%)
Pulmonary Regurgitation by TTE	
None	4 / 78 (5.1%)
Trace	2 / 78 (2.6%)
Mild	1 / 78 (1.3%)
Moderate	5 / 78 (6.4%)
Severe	66 / 78 (84.6%)

Categorical measures-No. / Total no. (%)

Continuous measures- Mean ± SD (N); Median (Min, Max)

The primary etiologies requiring reconstruction of the RVOT and placement of a pulmonary conduit for the safety population were as follows:

- Tetralogy of Fallot, 42%
- Aortic Valve Defect/Disease Resulting in Ross Procedure, 33%
- Truncus Arteriosus, 6%
- Pulmonary Stenosis, 5%
- Transposition of the Great Arteries, 5%
- Pulmonary Atresia, 5%
- Other/Unknown, 4%

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the valve implanted cohort of 69 patients available for the 1 year evaluation. The primary endpoint was freedom from device- or procedure-related death and/or reintervention at 1 year (**Table 7**) which met the pre-specified performance goal of 75%. The key safety outcomes for this study are presented below in **Tables 7 to 8** and **Figures 6 to 10**. Adverse effects are reported in **Tables 9 and 10**.

Table 7: Freedom from Device- or Procedure-Related Death and/or Reintervention at 1 Year (Valve Implant Population)

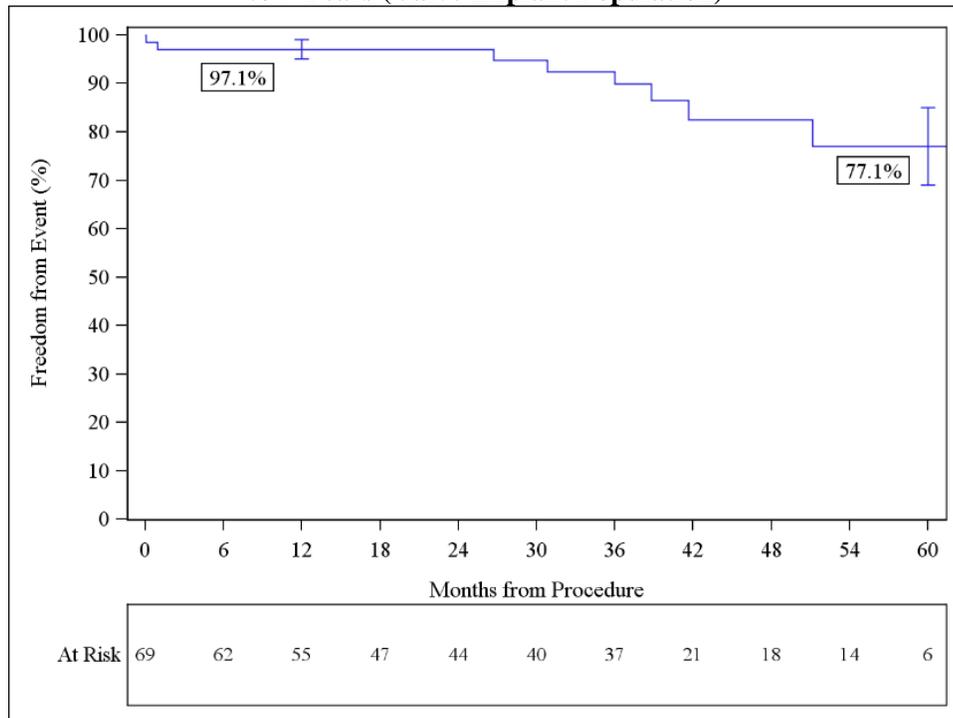
Adverse Event	Events	Patients with Event	Patients at Risk	KM Estimate [1]	Standard Error [2]	95% Confidence Interval
Device- or Procedure-Related Death and/or Reintervention	3	2	55	0.971	0.020	(0.889, 0.993)
Device- or Procedure-Related Death	0	0	57	1.000	0.000	NA
Reintervention	3	2	55	0.971	0.020	(0.889, 0.993)

[1] Kaplan-Meier survival estimates are calculated at 1 year and use the first event per patient. 1 Year is taken to mean 365.25 days. Any event occurring after 1 year is not included.

[2] Standard error of the survival estimate at 1 year.

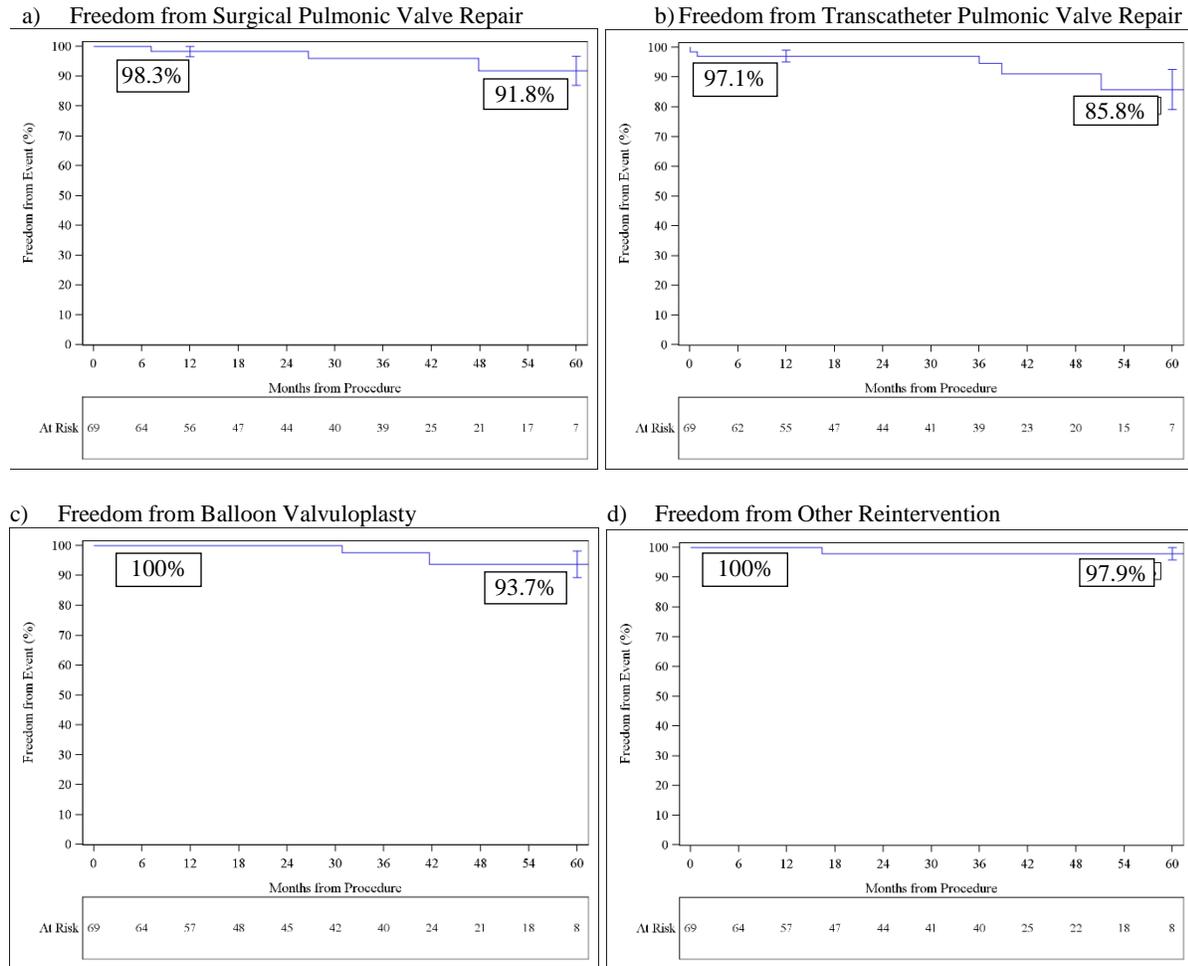
At 5 years, the freedom from device- or procedure-related death and/or reintervention was 77.1% (**Figure 6**). As there were no device- or procedure-related patient deaths at 5 years, the incidence of reinterventions solely contributed to the KM estimate.

Figure 6: Freedom from Device- or Procedure-Related Death and/or Reintervention to 5 Years (Valve Implant Population)



Freedom from reintervention to 5 years for the valve implant population is shown in **Figure 7**, stratified by type of reintervention: a) freedom from surgical pulmonic valve repair was 98.3% at 1 year and 91.8% at 5 years; b) freedom from transcatheter pulmonic valve implantation was 97.1% at 1 year and 85.8% at 5 years; c) freedom from balloon valvuloplasty was 100% at 1 year and 93.7% at 5 years; and d) freedom from other types of reintervention was 100% at 1 year and 97.9% at 5 years.

Figure 7: Freedom from Reintervention by Type of Reintervention to 5 Years (Valve Implanted Population)



Freedom from MACCE at 6 months in the valve implant population was 94.1% (Table 8).

Table 8: Freedom from MACCE at 6 Months (Valve Implant Population)

Adverse Event	Events	Patients with Event	Patients at Risk	KM Estimate [1]	Standard Error [2]
MACCE	4	4	60	0.941	0.028
All-cause mortality	0	0	64	1.000	0.000
Myocardial infarction	0	0	64	1.000	0.000
Reintervention	2	2	62	0.971	0.020
Vascular injury	1	1	63	0.986	0.014
Stroke	0	0	64	1.000	0.000
Pulmonary embolism	1	1	63	0.985	0.015

[1] Kaplan-Meier survival estimates are calculated at 6 months and use the first event per patient. Six months is taken to mean 180 days. Events occurring after 6 months are not included in this analysis.

[2] Standard error of the survival estimate at 6 months.

Adverse effects that occurred in the PMA clinical study:

The site-reported serious adverse events in the Safety Population are presented in **Table 9**.

Table 9: Incidence of Site-Reported Serious Adverse Events by Study Visit (with CEC adjudication where available) in the Safety Population (N=79)

Adverse Event	≤ 30 Days		31 – 365 Days		All Events	
	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event
Any Serious Adverse Event	29	3/ 79 (29.1%)	22	13/ 79 (16.5%)	132	38/ 79 (48.1%)
Other	2	2/ 79 (2.5%)	10	6/ 79 (7.6%)	37	13/ 79 (16.5%)
Infection (excluding endocarditis)	1	1/ 79 (1.3%)	3	3/ 79 (3.8%)	12	7/ 79 (8.9%)
CHF	1	1/ 79 (1.3%)	0	0/ 79 (0.0%)	11	4/ 79 (5.1%)
Electrolyte and/or CBC and platelet counts abnormal	1	1/ 79 (1.3%)	2	1/ 79 (1.3%)	11	2/ 79 (2.5%)
Valve stenosis	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)	9	6/ 79 (7.6%)
Arrhythmia	2	2/ 79 (2.5%)	0	0/ 79 (0.0%)	8	6/ 79 (7.6%)
Endocarditis	1	1/ 79 (1.3%)	2	2/ 79 (2.5%)	5	4/ 79 (5.1%)
Pulmonary artery perforation – rupture of RVOT conduit	5	5/ 79 (6.3%)	0	0/ 79 (0.0%)	5	5/ 79 (6.3%)
Fever	3	3/ 79 (3.8%)	0	0/ 79 (0.0%)	4	4/ 79 (5.1%)
Hemorrhage requiring transfusion	2	2/ 79 (2.5%)	1	1/ 79 (1.3%)	3	3/ 79 (3.8%)
Syncope	0	0/ 79 (0.0%)	0	0/ 79 (0.0%)	3	3/ 79 (3.8%)
Valve damage or dysfunction	2	2/ 79 (2.5%)	0	0/ 79 (0.0%)	3	3/ 79 (3.8%)
Device migration	2	2/ 79 (2.5%)	0	0/ 79 (0.0%)	2	2/ 79 (2.5%)
Hematoma	2	2/ 79 (2.5%)	0	0/ 79 (0.0%)	2	2/ 79 (2.5%)
Respiratory complication	1	1/ 79 (1.3%)	0	0/ 79 (0.0%)	2	2/ 79 (2.5%)
Anemia	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)	1	1/ 79 (1.3%)
Angina	0	0/ 79 (0.0%)	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)
Atelectasis	1	1/ 79 (1.3%)	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)
Bleeding Event	1	1/ 79 (1.3%)	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)
Dyspnea	0	0/ 79 (0.0%)	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)
Embolism: air or thrombus	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)	1	1/ 79 (1.3%)
Hemolysis	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)	1	1/ 79 (1.3%)
Hemorrhagic event	0	0/ 79 (0.0%)	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)
Hypotension	1	1/ 79 (1.3%)	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)
Ischemia	0	0/ 79 (0.0%)	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)
MI	0	0/ 79 (0.0%)	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)
Neurological Event (including TIA, stroke and psychomotor deficit)	0	0/ 79 (0.0%)	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)
Non-emergent reoperation	0	0/ 79 (0.0%)	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)
Nonstructural valve dysfunction	1	1/ 79 (1.3%)	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)
Thromboembolism	0	0/ 79 (0.0%)	0	0/ 79 (0.0%)	1	1/ 79 (1.3%)

Summary statistics:
Categorical measures-No. / Total no. (%)

Seriousness was determined by the CEC for these events if they have been adjudicated and the site otherwise.

Note: The rates given in the All Events columns are cumulative based on all events reported by all patients up to their current follow-up time including 10 patients who completed 5 year follow-up.

Two patients experienced a device migration (2/79, 2.5%) early in the trial. The instructions for use were modified; no other device migrations occurred in the trial after this modification. Serious Adverse Events (SAE) for RVOT conduit ruptures occurred in 5/79 (6.3%) patients. These 5 ruptures were related to balloon valvuloplasty or placement of a pre-stent and no ruptures occurred during placement of the SAPIEN THV.

CEC adjudicated endpoint adverse events up to 5 years are presented in **Table 10**.

Table 10: CEC-adjudicated Endpoint adverse events in the Valve Implanted Population (N=69)

Outcome [a]	30 Days (patients at risk=69) [k]		1 Year (patients at risk=57) [k]		2 Year (patients at risk=45) [k]		3 Years (patients at risk=41) [k]		4 Years (patients at risk=23) [k]		5 Years (patients at risk=9) [k]	
	KM Survival Estimate [j]	Patients With Event	KM Survival Estimate [j]	Patients With Event	KM Survival Estimate [j]	Patients With Event	KM Survival Estimate [j]	Patients With Event	KM Survival Estimate [j]	Patients With Event	KM Survival Estimate [j]	Patients With Event
Valve Dysfunction [b]	0.957	3	0.942	4	0.885	7	0.772	12	0.707	14	0.657	15
MACCE [c]	0.971	2	0.941	4	0.919	5	0.825	9	0.751	11	0.697	12
Device or Procedure Related Death or Reintervention	0.971	2	0.971	2	0.971	2	0.900	5	0.826	7	0.771	8
Reintervention	0.971	2	0.971	2	0.971	2	0.900	5	0.826	7	0.771	8
Transcatheter pulmonic valve implantation (TPVI or V-in-V)	0.971	2	0.971	2	0.971	2	0.947	3	0.912	4	0.858	5
Endocarditis (site) [d]	0.986	1	0.970	2	0.970	2	0.970	2	0.933	3	0.871	4
Surgical Pulmonic Valve Repair / Replacement	1.000	0	0.983	1	0.983	1	0.960	2	0.918	3	0.918	3
Balloon valvuloplasty	1.000	0	1.000	0	1.000	0	0.976	1	0.937	2	0.937	2
Deaths	1.000	0	1.000	0	0.978	1	0.978	1	0.978	1	0.978	1
Death from cardiovascular cause [e]	1.000	0	1.000	0	0.978	1	0.978	1	0.978	1	0.978	1
Myocardial infarction	1.000	0	1.000	0	1.000	0	0.976	1	0.976	1	0.976	1
Other reintervention [f]	1.000	0	1.000	0	0.979	1	0.979	1	0.979	1	0.979	1
Vascular Injury [g]	1.000	0	0.986	1	0.986	1	0.986	1	0.986	1	0.986	1
Pulmonary embolism	1.000	0	0.985	1	0.985	1	0.985	1	0.985	1	0.985	1
Device or procedure related death	1.000	0	1.000	0	1.000	0	1.000	0	1.000	0	1.000	0
Stroke	1.000	0	1.000	0	1.000	0	1.000	0	1.000	0	1.000	0
Study Valve Stent Fracture (site) [d,h]	1.000	0	1.000	0	1.000	0	1.000	0	1.000	0	1.000	0

Summary statistics: n/N (%) of Patients

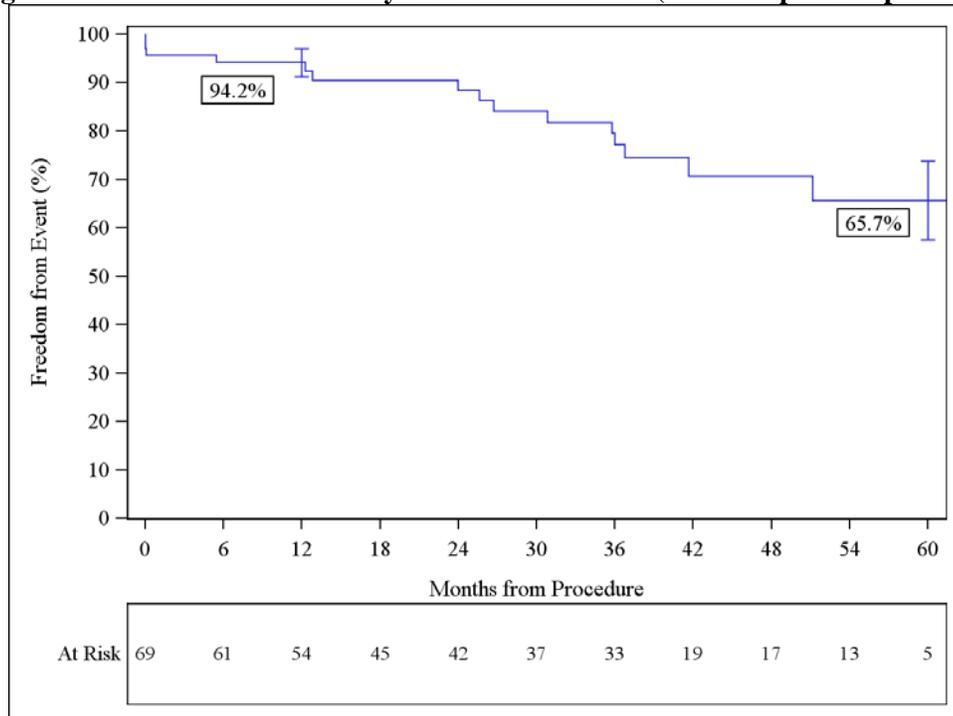
[a] CEC-adjudicated

[b] Valve Dysfunction is a non-hierarchical composite of the following events: all-cause mortality, surgical pulmonary valve replacement, valve frame fracture, recurrent pulmonary stenosis, moderate/severe regurgitation and reintervention.

- [c] MACCE is a non-hierarchical composite of the following events: all-cause mortality, myocardial infarction, reintervention, vascular injury, stroke and pulmonary embolism.
- [d] Site-reported events.
- [e] Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
- [f] The other consists of a patient that underwent successful stenting of stenotic, surgically placed conduit.
- [g] Vascular injury resulting in the need for an unplanned vascular intervention.
- [h] A study valve fracture is a fracture of the frame of the study valve.
- [j] Kaplan-Meier rates are provided at the time point specified. Any events occurring after are not included.
- [k] Patients at risk are the number of patients with at least as many days on study as the time point. 1 Year is taken to mean 365.25 days.

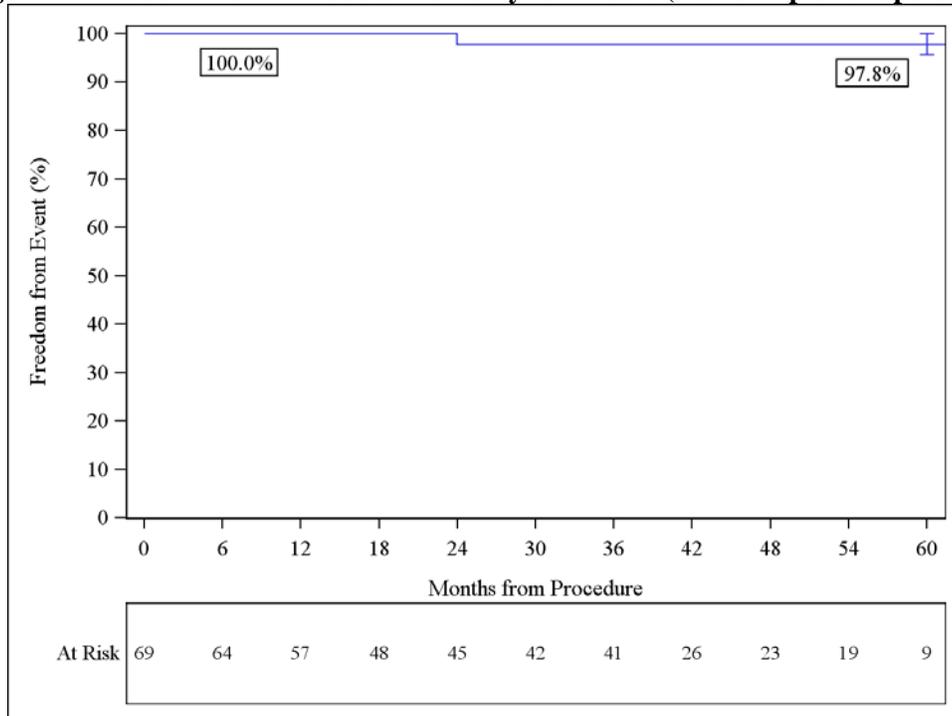
Valve dysfunction is a non-hierarchical composite of all-cause mortality, surgical pulmonary valve replacement, valve frame fracture, recurrent pulmonary stenosis, moderate/severe regurgitation and reintervention. Freedom from valve dysfunction is presented in **Figure 8**.

Figure 8: Freedom from Valve Dysfunction to 5 Years (Valve Implant Population)



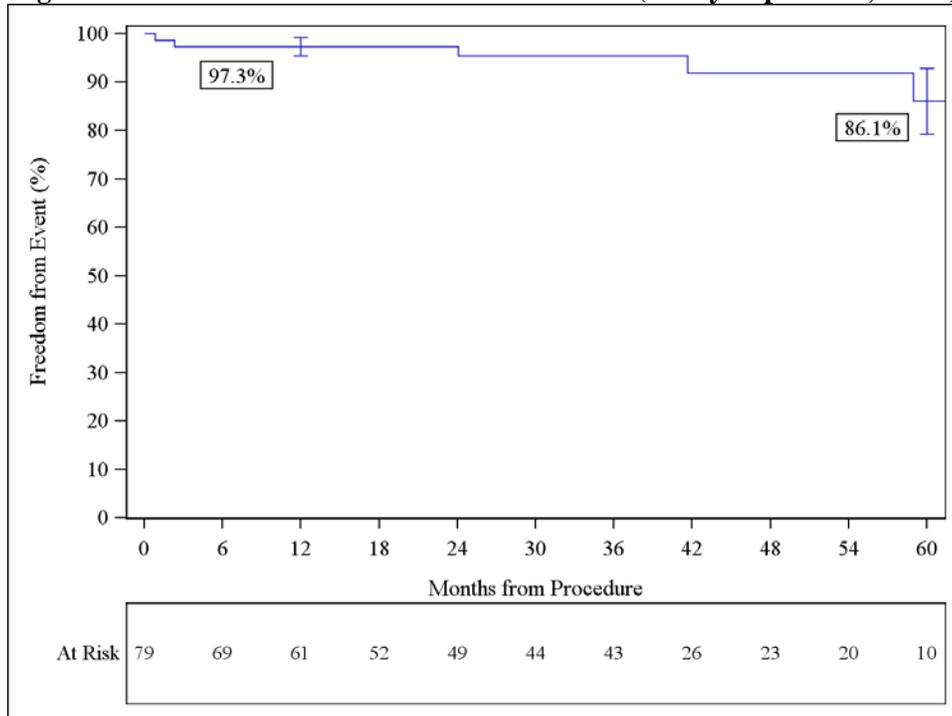
Freedom from all-cause mortality for the valve implant population is presented in **Figure 9**.

Figure 9: Freedom from All-Cause Mortality to 5 Years (Valve Implant Population)



Freedom from endocarditis for the safety population is presented in **Figure 10**. Patients that were pre-stented had an observed rate of endocarditis of 4.2% (3/71) whereas patients that were not pre-stented had no reported endocarditis (0/7). Due to the small number of patients that were not pre-stented, no statistical conclusions may be made from this data.

Figure 10: Freedom from Endocarditis at 5 Years (Safety Population, N=79)



2. Effectiveness Results

The analysis of effectiveness was based on the 69 evaluable patients. Key effectiveness outcomes are presented in **Tables 11 to 12** and **Figures 11 to 17**.

Overall device success for the attempted implant population (**Table 11**) was 95.2% and reflects cases with successful “valve deployed in target area” and “regurgitation mild or less.”

Table 11: Device Success (Attempted Implant Population)

	No. / Total no. (%)
Overall Device Success [1]	59/62 (95.2%)
Valve Deployed in Target Area	69/70 (98.6%)
Regurgitation mild or less [2]	60/62 (96.8%)

[1] Device success is defined as deployment of the valve to the target area and removal of the delivery catheter out of the body and improvement in PR to none, trace, or mild per the earliest evaluable echocardiogram. The earliest available echocardiogram is the first echocardiogram a participant received after the index procedure that has non missing regurgitation data.

[2] Echocardiograms with regurgitation data were available for 62 of the 70 patients in the attempted implant population.

Overall Functional Improvement at 6 Months

Functional improvement at 6 months for patients in the valve implant population is presented in **Table 12**. A decrease in pulmonary regurgitation to mild or less was observed in 96.2% of patients; improved pulmonary stenosis mean gradient was

93.8%; functional improvement in NYHA was 92.2%; and freedom from recurrent pulmonary stenosis was 100%.

Table 12: Overall Functional Improvement at 6 Months (Valve Implant Population)

Functional Improvement	Summary Statistics
Overall Functional Improvement [1]	51 / 58 (87.9%)
Improved Pulmonary Regurgitation [a]	51 / 53 (96.2%)
Improved Mean Gradient [b]	15 / 16 (93.8%)
Functional Improvement in NYHA [c]	47 / 51 (92.2%)
Freedom from Recurrent Pulmonary Stenosis [d]	56 / 56 (100.0%)

Summary statistics: Categorical measures-No. / Total no. (%)

[1] Overall functional improvement, as defined by the following 4 categories:

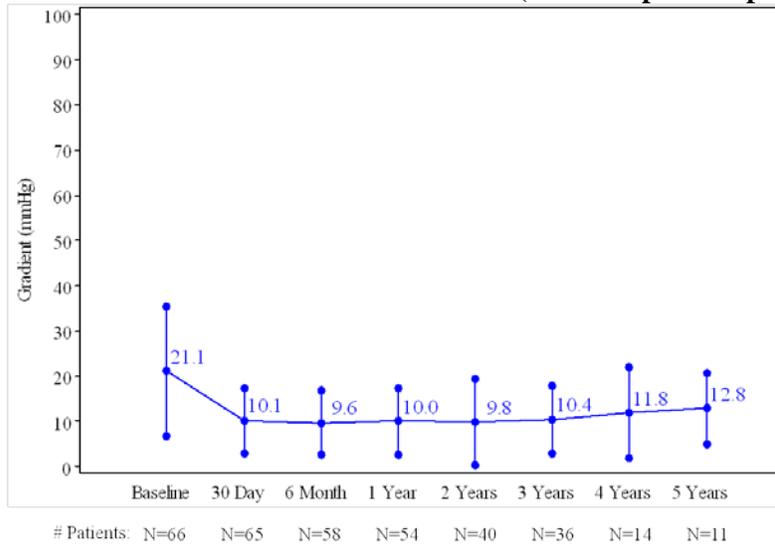
- a) Improved valve function demonstrated by a decrease in PR to mild or less per TTE at 6 months for patients with moderate or more PR at baseline
- b) Improved valve function demonstrated by a decrease in pulmonary stenosis mean gradient to <30mmHg for patients with pulmonary stenosis mean gradient >30mmHg at baseline.
- c) Functional improvement from baseline of ≥ 1 NYHA functional class at 6 months for patients with baseline NYHA functional class ≥ 2
- d) Freedom from recurrent pulmonary stenosis at 6 months

For patients with mild or less PR at baseline only categories b, c, and d were used to determine overall functional improvement. For patients with pulmonary stenosis mean gradient <30mmHg at baseline only categories a, c, and d were used for overall functional improvement. For patients with NYHA functional class of <2 at baseline only categories a, b, and d were used to determine overall functional improvement. For patients treated for indications other than pulmonary stenosis only categories a, b, and c for overall functional improvement were used.

Valve Performance

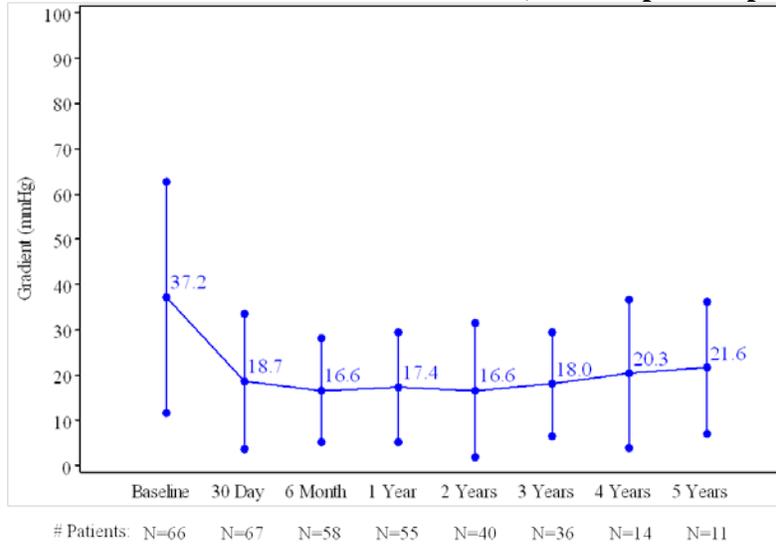
Improvement in conduit mean gradient was demonstrated, as it decreased from 21.1±14.3 mmHg at baseline to 10.1±7.2 mmHg at 30 days 10.0 ± 7.3 mmHg at 1 year and 12.8±7.8 mmHg at 5 years (**Figure 11**).

Figure 11: Conduit Mean Gradient to 5 Years (Valve Implant Population)



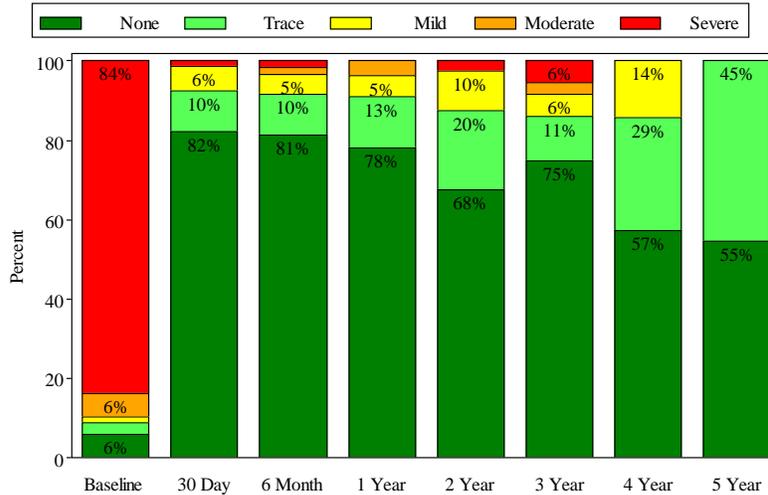
An improvement in conduit peak gradient was demonstrated, as it decreased from 37.2±25.5 mmHg at baseline to 18.7±15.0 mmHg at 30 days, 17.4 ± 12.1 mmHg at 1 year and 21.6±14.5 mmHg at 5 years (**Figure 12**).

Figure 12: Conduit Peak Gradient to 5 Years (Valve Implant Population)



Total pulmonic regurgitation by grade to 5 years is presented in **Figure 13**. Moderate/severe pulmonic regurgitation decreased from 90% at baseline to 2% at 30 days, 4 % at 1 year and 0% at 5 years.

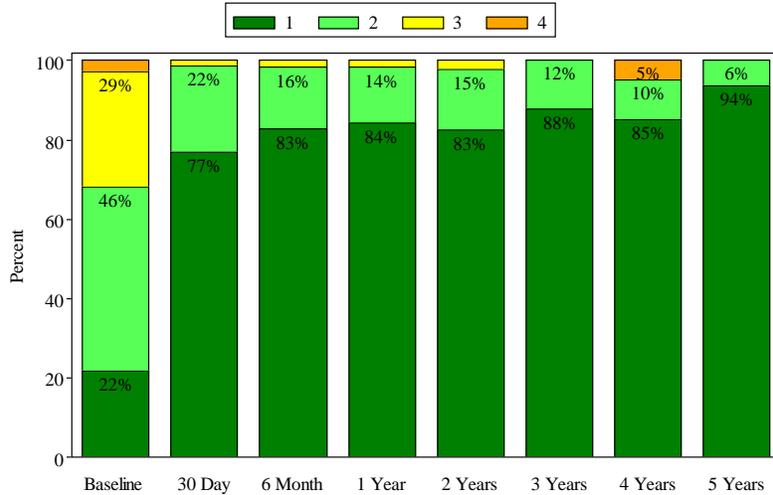
Figure 13: Total Pulmonic Regurgitation by Grade to 5 Years (Valve Implant Population)



New York Heart Association (NYHA)

NYHA classification by visit for the valve implant population is shown in **Figure 14**. There was a trend showing patient functional improvement over time, as 22% of the patients were in NYHA class 1 at baseline, 84% at 1 year and 94% at 5 years.

Figure 14: NYHA Classification by Visit (Valve Implant Population)



3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: concomitant pre-stenting, age, and valve size.

Analysis by Pre-Stenting

Adjunctive analyses of safety and effectiveness stratified by patients who received a pre-stent and those that did not receive a pre-stent were performed.

Pre-stenting of the RVOT landing zone for the SAPIEN THV was performed during the IDE study, at the discretion of the treating physician. The protocol did not specify any criteria for how or when to perform the pre-stenting procedure. Therefore, the data presented below represents the outcomes of subjects who were implanted with a variety (in number and type) of stents along with the SAPIEN THV.

In total, 91.0% (71/78) of patients had pre-stenting of the RVOT conduit, either prior to or during the implant procedure. Therefore the analyses were limited by the size difference between these groups. The site-reported serious adverse events from the COMPASSION trial stratified by pre-stenting status is shown in **Table 13**. Note that this study was not designed to investigate the differences in outcomes between patients with and without pre-stenting, nor was it designed to investigate whether stents used to pre-stent the RVOT landing site are safe and effective for this use.

Table 13: Site Reported Serious Adverse Events for Patients with and Without Pre-Stenting

Adverse Event	No Stent (N=7)						Stented (N=71)					
	≤ 30 Days		31 – 365 Days		All Events		≤ 30 Days		31 – 365 Days		All Events	
	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event
Any Serious Adverse Event	1	1/7(14.3%)	0	0/7 (0.0%)	5	3/7 (42.9%)	27	21/ 71 (29.6%)	22	13/ 71 (18.3%)	125	34/ 71 (47.9%)
Other	0	0/7(0.0%)	0	0/7 (0.0%)	1	1/7 (14.3%)	1	1/ 71 (1.4%)	10	6/ 71 (8.5%)	35	11/ 71 (15.5%)
Infection (excluding endocarditis)	0	0/7(0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	1	1/ 71 (1.4%)	3	3/ 71 (4.2%)	12	7/ 71 (9.9%)
CHF	0	0/7(0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	1	1/ 71 (1.4%)	0	0/ 71 (0.0%)	11	4/ 71 (5.6%)
Electrolyte and/or CBC and platelet counts abnormal	0	0/7(0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	1	1/ 71 (1.4%)	2	1/ 71 (1.4%)	11	2/ 71 (2.8%)
Valve stenosis	0	0/7(0.0%)	0	0/7 (0.0%)	2	1/7 (14.3%)	0	0/ 71 (0.0%)	1	1/ 71 (1.4%)	7	5/ 71 (7.0%)
Arrhythmia	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	2	2/ 71 (2.8%)	0	0/ 71 (0.0%)	8	6/ 71 (8.5%)
Pulmonary artery perforation – rupture of RVOT conduit	1	1/7 (14.3%)	0	0/7 (0.0%)	1	1/7 (14.3%)	4	4/ 71 (5.6%)	0	0/ 71 (0.0%)	4	4/ 71 (5.6%)
Endocarditis	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	1	1/ 71 (1.4%)	2	2/ 71 (2.8%)	4	3/ 71 (4.2%)
Fever	0	0/7(0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	3	3/ 71 (4.2%)	0	0/ 71 (0.0%)	4	4/ 71 (5.6%)
Hemorrhage requiring transfusion	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	2	2/ 71 (2.8%)	1	1/ 71 (1.4%)	3	3/ 71 (4.2%)
Syncope	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/ 71 (0.0%)	0	0/ 71 (0.0%)	3	3/ 71 (4.2%)
Valve damage or dysfunction	0	0/7 (0.0%)	0	0/7 (0.0%)	1	1/7 (14.3%)	2	2/ 71 (2.8%)	0	0/ 71 (0.0%)	2	2/ 71 (2.8%)
Device migration	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	2	2/ 71 (2.8%)	0	0/ 71 (0.0%)	2	2/ 71 (2.8%)
Hematoma	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	2	2/ 71 (2.8%)	0	0/ 71 (0.0%)	2	2/ 71 (2.8%)
Respiratory complication	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	1	1/ 71 (1.4%)	0	0/ 71 (0.0%)	2	2/ 71 (2.8%)
Anemia	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/ 71 (0.0%)	1	1/ 71 (1.4%)	1	1/ 71 (1.4%)
Angina	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/ 71 (0.0%)	0	0/ 71 (0.0%)	1	1/ 71 (1.4%)
Atelectasis	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	1	1/ 71 (1.4%)	0	0/ 71 (0.0%)	1	1/ 71 (1.4%)
Bleeding Event	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	1	1/ 71 (1.4%)	0	0/ 71 (0.0%)	1	1/ 71 (1.4%)
Dyspnea	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/ 71 (0.0%)	0	0/ 71 (0.0%)	1	1/ 71 (1.4%)
Embolism: air or thrombus	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/ 71 (0.0%)	1	1/ 71 (1.4%)	1	1/ 71 (1.4%)
Hemolysis	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/ 71 (0.0%)	1	1/ 71 (1.4%)	1	1/ 71 (1.4%)
Hemorrhagic event	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/ 71 (0.0%)	0	0/ 71 (0.0%)	1	1/ 71 (1.4%)
Hypotension	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	1	1/ 71 (1.4%)	0	0/ 71 (0.0%)	1	1/ 71 (1.4%)

Adverse Event	No Stent (N=7)						Stented (N=71)					
	≤ 30 Days		31 – 365 Days		All Events		≤ 30 Days		31 – 365 Days		All Events	
	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event
Ischemia	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/71 (0.0%)	0	0/71 (0.0%)	1	1/71 (1.4%)
MI	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/71 (0.0%)	0	0/71 (0.0%)	1	1/71 (1.4%)
Neurological Event (including TIA, stroke and psychomotor deficit)	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/71 (0.0%)	0	0/71 (0.0%)	1	1/71 (1.4%)
Non-emergent reoperation	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/71 (0.0%)	0	0/71 (0.0%)	1	1/71 (1.4%)
Nonstructural valve dysfunction	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	1	1/71 (1.4%)	0	0/71 (0.0%)	1	1/71 (1.4%)
Thromboembolism	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/7 (0.0%)	0	0/71 (0.0%)	0	0/71 (0.0%)	1	1/71 (1.4%)

Summary statistics:

Categorical measures-No. / Total no. (%)

Seriousness was determined by the CEC for these events if they have been adjudicated and the site otherwise.

Note: The rates given in the All Events columns are cumulative based on all events reported by all patients up to their current follow-up time including 10 patients reaching the 5 year follow-up.

Analysis by Patient Age

Adjunctive analyses of safety and effectiveness stratified by patients aged 21 years or younger at baseline versus patients aged 22 years or older at baseline was conducted. The COMPASSION study was not designed to investigate the differences in outcomes between age groups and therefore statistical inferences cannot be made for this analysis. Site reported SAEs by baseline age group are shown in **Table 14**.

Table 14: Site-Reported Serious Adverse Events by Baseline Age group in the Safety Population

Adverse Event	Age 21 Years or Younger (N=29)						Age 22 Years or Older (N=50)					
	≤ 30 Days		31 – 365 Days		All Events		≤ 30 Days		31 – 365 Days		All Events	
	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event
Any Serious Adverse Event	11	8/29 (27.6%)	4	4/29 (13.8%)	35	15/29 (51.7%)	18	15/50 (30.0%)	18	9/50 (18.0%)	97	23/50 (46.0%)
Other	0	0/29 (0.0%)	1	1/29 (3.4%)	8	3/29 (10.3%)	2	2/50 (4.0%)	9	5/50 (10.0%)	29	10/50 (20.0%)
Infection (excluding endocarditis)	1	1/29 (3.4%)	1	1/29 (3.4%)	2	2/29 (6.9%)	0	0/50 (0.0%)	2	2/50 (4.0%)	10	5/50 (10.0%)
CHF	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	1	1/50 (2.0%)	0	0/50 (0.0%)	11	4/50 (8.0%)
Electrolyte and/or CBC and platelet counts abnormal	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	1	1/50 (2.0%)	2	1/50 (2.0%)	11	2/50 (4.0%)
Valve stenosis	0	0/29 (0.0%)	1	1/29 (3.4%)	5	4/29 (13.8%)	0	0/50 (0.0%)	0	0/50 (0.0%)	4	2/50 (4.0%)
Arrhythmia	0	0/29 (0.0%)	0	0/29 (0.0%)	1	1/29 (3.4%)	2	2/50 (4.0%)	0	0/50 (0.0%)	7	5/50 (10.0%)
Endocarditis	1	1/29 (3.4%)	1	1/29 (3.4%)	3	2/29 (6.9%)	0	0/50 (0.0%)	1	1/50 (2.0%)	2	2/50 (4.0%)
Pulmonary artery perforation – rupture of RVOT conduit	2	2/29 (6.9%)	0	0/29 (0.0%)	2	2/29 (6.9%)	3	3/50 (6.0%)	0	0/50 (0.0%)	3	3/50 (6.0%)
Fever	2	2/29 (6.9%)	0	0/29 (0.0%)	3	3/29 (10.3%)	1	1/50 (2.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)
Hemorrhage requiring transfusion	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	2	2/50 (4.0%)	1	1/50 (2.0%)	3	3/50 (6.0%)

Adverse Event	Age 21 Years or Younger (N=29)						Age 22 Years or Older (N=50)					
	≤ 30 Days		31 – 365 Days		All Events		≤ 30 Days		31 – 365 Days		All Events	
	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event
Syncope	0	0/29 (0.0%)	0	0/29 (0.0%)	2	2/29 (6.9%)	0	0/50 (0.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)
Valve damage or dysfunction	1	1/29 (3.4%)	0	0/29 (0.0%)	2	2/29 (6.9%)	1	1/50 (2.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)
Device migration	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	2	2/50 (4.0%)	0	0/50 (0.0%)	2	2/50 (4.0%)
Hematoma	2	2/29 (6.9%)	0	0/29 (0.0%)	2	2/29 (6.9%)	0	0/50 (0.0%)	0	0/50 (0.0%)	0	0/50 (0.0%)
Respiratory complication	0	0/29 (0.0%)	0	0/29 (0.0%)	1	1/29 (3.4%)	1	1/50 (2.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)
Anemia	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)	1	1/50 (2.0%)
Angina	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/50 (0.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)
Atelectasis	1	1/29 (3.4%)	0	0/29 (0.0%)	1	1/29 (3.4%)	0	0/50 (0.0%)	0	0/50 (0.0%)	0	0/50 (0.0%)
Bleeding Event	1	1/29 (3.4%)	0	0/29 (0.0%)	1	1/29 (3.4%)	0	0/50 (0.0%)	0	0/50 (0.0%)	0	0/50 (0.0%)
Dyspnea	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/50 (0.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)
Embolism: air or thrombus	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)	1	1/50 (2.0%)
Hemolysis	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)	1	1/50 (2.0%)
Hemorrhagic event	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/50 (0.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)
Hypotension	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	1	1/50 (2.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)
Ischemia	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/50 (0.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)
MI	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/50 (0.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)
Neurological Event (including TIA, stroke and psychomotor deficit)	0	0/29 (0.0%)	0	0/29 (0.0%)	1	1/29 (3.4%)	0	0/50 (0.0%)	0	0/50 (0.0%)	0	0/50 (0.0%)
Non-emergent reoperation	0	0/29 (0.0%)	0	0/29 (0.0%)	1	1/29 (3.4%)	0	0/50 (0.0%)	0	0/50 (0.0%)	0	0/50 (0.0%)
Nonstructural valve dysfunction	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	1	1/50 (2.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)
Thromboembolism	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/29 (0.0%)	0	0/50 (0.0%)	0	0/50 (0.0%)	1	1/50 (2.0%)

Summary statistics:

Categorical measures-No. / Total no. (%)

Seriousness was determined by the CEC for these events if they have been adjudicated and the site otherwise.

Note: The rates given in the All Events columns are cumulative based on all events reported by all patients up to their current follow-up time including 10 patients reaching the 5 year follow-up.

CEC adjudicated freedom from MACCE stratified by baseline age group is shown in **Table 15** for the valve implanted population.

Table 15: CEC Adjudicated Freedom from MACCE by Baseline Age group in the Valve Implanted Population

Age group	Adverse Event	Kaplan-Meier Survival Estimate [1]						
		30 Days (Patients at risk=69) [4]	6 Months (Patients at risk=69) [4]	1 Year (Patients at risk=69) [4]	2 Years (Patients at risk=69) [4]	3 Years (Patients at risk=69) [4]	4 Years (Patients at risk=69) [4]	5 Years (Patients at risk=69) [4]
Age 21 or Younger (N=27)	MACCE [2]	0.963	0.963	0.963	0.963	0.856	0.770	0.642
	All-Cause Mortality	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Myocardial infarction	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Reintervention	0.963	0.963	0.963	0.963	0.856	0.770	0.642
	Vascular Injury [3]	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Stroke	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Pulmonary embolism	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Age 22 or Older (N=42)	MACCE [2]	0.976	0.928	0.928	0.891	0.806	0.744	0.744
	All-Cause Mortality	1.000	1.000	1.000	0.963	0.963	0.963	0.963
	Myocardial infarction	1.000	1.000	1.000	1.000	0.957	0.957	0.957
	Reintervention	0.976	0.976	0.976	0.976	0.934	0.871	0.871
	Vascular Injury [3]	1.000	0.976	0.976	0.976	0.976	0.976	0.976
	Stroke	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Pulmonary embolism	1.000	0.976	0.976	0.976	0.976	0.976	0.976

[1] Kaplan-Meier survival estimates are calculated at each time point and use the first event per patient. 6 months is taken to mean 180 days, and 1 year is taken to mean 365.25 days. Events occurring after the time point are not included in the analysis.

[2] MACCE is a non-hierarchical composite of the following events: All-cause mortality, myocardial infarction, reintervention, vascular injury, stroke, and pulmonary embolism

[3] Vascular injury resulting in the need for an unplanned vascular intervention

[4] Patients at risk are the number of patients with at least as many days on study as the time point. 1 Year is taken to mean 365.25 days.

Overall functional improvement at 6 months by Baseline age group in the Valve Implanted population is shown in **Table 16**.

Table 16: Functional Improvement at 6 months by age group at baseline

Functional Improvement	Age 21 or Younger (N=27)	Age 22 or Older (N=42)
Overall Functional Improvement [1]	17 / 22 (77.3%)	34 / 36 (94.4%)
Improved Valve Function [a]	19 / 20 (95.0%)	32 / 33 (97.0%)
Functional Improvement in NYHA [b]	11 / 14 (78.6%)	36 / 37 (97.3%)
Freedom from Recurrent Pulmonary Stenosis [c]	21 / 21 (100.0%)	35 / 35 (100.0%)
Improved Gradient [d]	7 / 8 (87.5%)	8 / 8 (100.0%)

Categorical measures-No. / Total no. (%)

[1] Overall functional improvement, as defined by the following 4 categories:

- a) Improved valve function demonstrated by a decrease in pulmonary regurgitation (PR) to mild or less ($\leq 2+$) per TTE at 6 months for patients with moderate or more ($> 2+$) PR at baseline
- b) Functional improvement from baseline of ≥ 1 NYHA functional class at 6 months for patients with baseline NYHA functional class ≥ 2
- c) Freedom from recurrent pulmonary stenosis at 6 months
- d) Improved valve function demonstrated by a decrease in pulmonary stenosis mean gradient to <30 mmHg for patients with pulmonary stenosis mean gradient >30 mmHg at baseline.

Patients with mild or less ($\leq 2+$) pulmonary regurgitation at baseline only use categories b, c, and d to determine overall functional improvement. Patients with NYHA functional class of <2 at baseline only use categories a, c, and d to determine overall functional improvement. Patients treated for indications other than pulmonary stenosis only use categories a, b, and d for overall functional improvement. Patients with pulmonary stenosis mean gradient <30 mmHg at baseline only use categories a, b, and c for overall functional improvement.

The improved valve function at 6 months in patients with high gradient at baseline age group for the VI population is shown in **Table 17**.

Table 17: Improved Valve Function at 6 Months in Patients with Mean Gradient >30 mmHg at Baseline by Age Group at Baseline

Mean Gradient	Age 21 or Younger (N=8)	Age 22 or Older (N=8)
Responder at 6 months [1]	7 / 8 (87.5%)	8 / 8 (100.0%)

Categorical measures-No. / Total no. (%)

[1] Mean gradient < 30mmHg at 6 months.

Improved NYHA functional class at 6 months for patients with baseline NYHA functional class ≥ 2 is shown in **Table 18**.

Table 18: Improved NYHA Functional Class at 6 Months in Patients with Baseline NYHA Functional Class ≥ 2 in the VI Population

NYHA Functional Class Change from Baseline	Age 21 or Younger (N=16)	Age 22 or Older (N=38)
Responder at 6 months [1]	11 / 14 (78.6%)	36 / 37 (97.3%)

Categorical measures-No. / Total no. (%)

[1] NYHA functional class improvement of at least 1 class at 6 months.

The overall functional improvement through 5 years of follow-up by age group for the VI population is shown in **Table 19**.

Table 19: Overall Functional Improvement through 5 Years of Follow-Up by Age Group for the Valve Implanted Population.

Age Group	Functional Improvement	30 Days	6 Months	1 Year	2 Years	3 Years	4 Years	5 Years
Age 21 or Younger (N=27)	Overall Functional Improvement [1]	23 / 26 (88.5%)	17 / 22 (77.3%)	18 / 21 (85.7%)	15 / 19 (78.9%)	13 / 18 (72.2%)	4 / 7 (57.1%)	3 / 7 (42.9%)
	Improved Valve Function [a]	21 / 22 (95.5%)	19 / 20 (95.0%)	19 / 19 (100.0%)	15 / 16 (93.8%)	13 / 15 (86.7%)	5 / 5 (100.0%)	5 / 5 (100.0%)
	Functional Improvement in NYHA [b]	14 / 16 (87.5%)	11 / 14 (78.6%)	13 / 14 (92.9%)	11 / 12 (91.7%)	11 / 12 (91.7%)	3 / 3 (100.0%)	4 / 4 (100.0%)
	Freedom from Recurrent Pulmonary Stenosis [c]	24 / 24 (100.0%)	21 / 21 (100.0%)	18 / 19 (94.7%)	17 / 18 (94.4%)	16 / 18 (88.9%)	6 / 9 (66.7%)	5 / 9 (55.6%)
	Improved Gradient [d]	9 / 10 (90.0%)	7 / 8 (87.5%)	7 / 8 (87.5%)	6 / 7 (85.7%)	5 / 6 (83.3%)	3 / 3 (100.0%)	3 / 3 (100.0%)
Age 22 or Older (N=42)	Overall Functional Improvement [1]	34 / 40 (85.0%)	34 / 36 (94.4%)	29 / 33 (87.9%)	20 / 23 (87.0%)	18 / 20 (90.0%)	8 / 11 (72.7%)	5 / 8 (62.5%)
	Improved Valve Function [a]	37 / 37 (100.0%)	32 / 33 (97.0%)	28 / 30 (93.3%)	20 / 20 (100.0%)	17 / 18 (94.4%)	7 / 7 (100.0%)	6 / 6 (100.0%)
	Functional Improvement in NYHA [b]	33 / 38 (86.8%)	36 / 37 (97.3%)	32 / 33 (97.0%)	23 / 24 (95.8%)	20 / 20 (100.0%)	12 / 13 (92.3%)	8 / 8 (100.0%)
	Freedom from Recurrent Pulmonary Stenosis [c]	36 / 36 (100.0%)	35 / 35 (100.0%)	31 / 31 (100.0%)	20 / 21 (95.2%)	16 / 18 (88.9%)	8 / 11 (72.7%)	7 / 10 (70.0%)
	Improved Gradient [d]	7 / 8 (87.5%)	8 / 8 (100.0%)	7 / 8 (87.5%)	2 / 3 (66.7%)	3 / 3 (100.0%)	2 / 2 (100.0%)	2 / 2 (100.0%)

Categorical measures-No. / Total no. (%)

[1] Overall functional improvement, as defined by the following 4 categories:

- a) Improved valve function demonstrated by a decrease in pulmonary regurgitation (PR) to mild or less per TTE at visit for patients with moderate or more (> 2) PR at baseline
- b) Functional improvement from baseline of ≥ 1 NYHA functional class at visit for patients with baseline NYHA functional class ≥ 2
- c) Freedom from recurrent pulmonary stenosis at visit

d) Improved valve function demonstrated by a decrease in pulmonary stenosis mean gradient to <30mmHg for patients with pulmonary stenosis mean gradient >30mmHg at baseline.
Patients with mild or less (<= 2+) pulmonary regurgitation at baseline only use categories b, c, and d to determine overall functional improvement. Patients with NYHA functional class of <2 at baseline only use categories a, c, and d to determine overall functional improvement. Patients treated for indications other than pulmonary stenosis only use categories a, b, and d for overall functional improvement. Patients with pulmonary stenosis mean gradient <30mmHg at baseline only use categories a, b, and c for overall functional improvement.

Analysis by Valve Size

Adjunctive analyses of safety and effectiveness stratified by valve size was conducted. The site-reported serious adverse events stratified by valve size are shown in **Table 20**. Note that this study was not designed to investigate the differences in outcomes between valve sizes.

Table 20: Incidence of Site-Reported Serious Adverse Events by Valve Size in the Safety Population

Adverse Event	23 mm Valve (N=48)						26 mm Valve (N=22)					
	≤ 30 Days		31 – 365 Days		All Events		≤ 30 Days		31 – 365 Days		All Events	
	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event	Events	Patients with Event
Any Serious Adverse Event	11	7/48 (14.6%)	9	7/48 (14.6%)	49	19/48 (39.6%)	12	10/22 (45.5%)	10	4/22 (18.2%)	72	13/22 (59.1%)
Other	0	0/48 (0.0%)	4	2/48 (4.2%)	12	5/48 (10.4%)	0	0/22 (0.0%)	5	3/22 (13.6%)	22	5/22 (22.7%)
Electrolyte and/or CBC and platelet counts abnormal	0	0/48 (0.0%)	0	0/48 (0.0%)	0	0/48 (0.0%)	1	1/22 (4.5%)	2	1/22 (4.5%)	11	2/22 (9.1%)
Infection (excluding endocarditis)	0	0/48 (0.0%)	1	1/48 (2.1%)	2	2/48 (4.2%)	1	1/22 (4.5%)	1	1/22 (4.5%)	9	4/22 (18.2%)
CHF	0	0/48 (0.0%)	0	0/48 (0.0%)	2	1/48 (2.1%)	0	0/22 (0.0%)	0	0/22 (0.0%)	7	2/22 (9.1%)
Valve stenosis	0	0/48 (0.0%)	1	1/48 (2.1%)	7	5/48 (10.4%)	0	0/22 (0.0%)	0	0/22 (0.0%)	2	1/22 (4.5%)
Arrhythmia	0	0/48 (0.0%)	0	0/48 (0.0%)	2	2/48 (4.2%)	2	2/22 (9.1%)	0	0/22 (0.0%)	6	4/22 (18.2%)
Endocarditis	1	1/48 (2.1%)	1	1/48 (2.1%)	3	2/48 (4.2%)	0	0/22 (0.0%)	1	1/22 (4.5%)	1	1/22 (4.5%)
Fever	1	1/48 (2.1%)	0	0/48 (0.0%)	2	2/48 (4.2%)	2	2/22 (9.1%)	0	0/22 (0.0%)	2	2/22 (9.1%)
Hemorrhage requiring transfusion	1	1/48 (2.1%)	1	1/48 (2.1%)	2	2/48 (4.2%)	1	1/22 (4.5%)	0	0/22 (0.0%)	1	1/22 (4.5%)
Syncope	0	0/48 (0.0%)	0	0/48 (0.0%)	2	2/48 (4.2%)	0	0/22 (0.0%)	0	0/22 (0.0%)	1	1/22 (4.5%)
Valve damage or dysfunction	2	2/48 (4.2%)	0	0/48 (0.0%)	3	3/48 (6.3%)	0	0/22 (0.0%)	0	0/22 (0.0%)	0	0/22 (0.0%)
Device migration	1	1/48 (2.1%)	0	0/48 (0.0%)	1	1/48 (2.1%)	1	1/22 (4.5%)	0	0/22 (0.0%)	1	1/22 (4.5%)
Hematoma	1	1/48 (2.1%)	0	0/48 (0.0%)	1	1/48 (2.1%)	1	1/22 (4.5%)	0	0/22 (0.0%)	1	1/22 (4.5%)
Pulmonary artery perforation – rupture of RVOT conduit	1	1/48 (2.1%)	0	0/48 (0.0%)	1	1/48 (2.1%)	1	1/22 (4.5%)	0	0/22 (0.0%)	1	1/22 (4.5%)
Respiratory complication	1	1/48 (2.1%)	0	0/48 (0.0%)	2	2/48 (4.2%)	0	0/22 (0.0%)	0	0/22 (0.0%)	0	0/22 (0.0%)
Angina	0	0/48 (0.0%)	0	0/48 (0.0%)	1	1/48 (2.1%)	0	0/22 (0.0%)	0	0/22 (0.0%)	0	0/22 (0.0%)
Atelectasis	1	1/48 (2.1%)	0	0/48 (0.0%)	1	1/48 (2.1%)	0	0/22 (0.0%)	0	0/22 (0.0%)	0	0/22 (0.0%)
Bleeding Event	1	1/48 (2.1%)	0	0/48 (0.0%)	1	1/48 (2.1%)	0	0/22 (0.0%)	0	0/22 (0.0%)	0	0/22 (0.0%)
Dyspnea	0	0/48 (0.0%)	0	0/48 (0.0%)	0	0/48 (0.0%)	0	0/22 (0.0%)	0	0/22 (0.0%)	1	1/22 (4.5%)
Embolism: air or thrombus	0	0/48 (0.0%)	0	0/48 (0.0%)	0	0/48 (0.0%)	0	0/22 (0.0%)	1	1/22 (4.5%)	1	1/22 (4.5%)
Hemolysis	0	0/48 (0.0%)	1	1/48 (2.1%)	1	1/48 (2.1%)	0	0/22 (0.0%)	0	0/22 (0.0%)	0	0/22 (0.0%)
Hemorrhagic event	0	0/48 (0.0%)	0	0/48 (0.0%)	0	0/48 (0.0%)	0	0/22 (0.0%)	0	0/22 (0.0%)	1	1/22 (4.5%)
Hypotension	0	0/48 (0.0%)	0	0/48 (0.0%)	0	0/48 (0.0%)	1	1/22 (4.5%)	0	0/22 (0.0%)	1	1/22 (4.5%)
Ischemia	0	0/48 (0.0%)	0	0/48 (0.0%)	0	0/48 (0.0%)	0	0/22 (0.0%)	0	0/22 (0.0%)	1	1/22 (4.5%)
MI	0	0/48 (0.0%)	0	0/48 (0.0%)	0	0/48 (0.0%)	0	0/22 (0.0%)	0	0/22 (0.0%)	1	1/22 (4.5%)
Neurological Event (including TIA, stroke and psychomotor deficit)	0	0/48 (0.0%)	0	0/48 (0.0%)	1	1/48 (2.1%)	0	0/22 (0.0%)	0	0/22 (0.0%)	0	0/22 (0.0%)
Non-emergent reoperation	0	0/48 (0.0%)	0	0/48 (0.0%)	1	1/48 (2.1%)	0	0/22 (0.0%)	0	0/22 (0.0%)	0	0/22 (0.0%)
Nonstructural valve dysfunction	0	0/48 (0.0%)	0	0/48 (0.0%)	0	0/48 (0.0%)	1	1/22 (4.5%)	0	0/22 (0.0%)	1	1/22 (4.5%)
Thromboembolism	0	0/48 (0.0%)	0	0/48 (0.0%)	1	1/48 (2.1%)	0	0/22 (0.0%)	0	0/22 (0.0%)	0	0/22 (0.0%)

Summary statistics:

Categorical measures-No. / Total no. (%)

Seriousness was determined by the CEC for these events if they have been adjudicated and the site otherwise.

Note: The rates given in the All Events columns are cumulative based on all events reported by all patients up to their current follow-up time including 10 patients reaching the 5 year follow-up.

A summary of freedom from CEC-adjudicated device- or procedure-related death and/or reintervention by valve size for the valve implanted population is shown in **Table 21**.

Table 21: CEC-Adjudicated freedom from Device- or Procedure-Related Death and/or Reintervention by Valve size in the Valve Implanted Population

Valve Size	Adverse Event	Kaplan-Meier Survival Estimate [1]						
		30 Days (Patients at risk=69) [2]	6 Months (Patients at risk=69) [2]	1 Year (Patients at risk=69) [2]	2 Years (Patients at risk=69) [2]	3 Years (Patients at risk=69) [2]	4 Years (Patients at risk=69) [2]	5 Years (Patients at risk=69) [2]
23mm (N=47)	Device or Procedure Related Death or Reintervention	0.979	0.979	0.979	0.979	0.874	0.822	0.754
	Device or Procedure Related Death	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Reintervention	0.979	0.979	0.979	0.979	0.874	0.822	0.754
26mm (N=22)	Device or Procedure Related Death or Reintervention	0.955	0.955	0.955	0.955	0.955	0.818	0.818
	Device or Procedure Related Death	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Reintervention	0.955	0.955	0.955	0.955	0.955	0.818	0.818

[1] Kaplan-Meier survival estimates are calculated at each study visit. 6 Months is taken to be 180 days and 1 year is taken to be 365.25 days. Events that occur after the time point are not included in the analysis.

[2] Patients at risk are the number of patients with at least as many days on study as the time point. 1 Year is taken to mean 365.25 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 conducting clinical studies covered by the regulation. The pivotal clinical study included 40 investigators of which none were full-time or part-time employees of the sponsor and one 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: 1 investigator
- 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. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Supplemental data to support the non-inferiority of the SAPIEN XT Transcatheter Heart Valve compared to the SAPIEN Transcatheter Heart Valve was previously summarized in the original P130009 SSED for the aortic indication. This SSED can be found at http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130009b.pdf.

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

In accordance with the provisions of section 515(c)(3) 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The COMPASSION Trial demonstrated that patients implanted with the SAPIEN transcatheter heart valve for treatment of a dysfunctional, non-compliant Right Ventricular Outflow Tract (RVOT) conduit are free from device- or procedure-related death and/or reintervention at 1 year. Long-term follow-up showed patients can remain free from device- or procedure-related death and/or reintervention for prolonged periods of time. Overall functional improvement was achieved acutely and adequately sustained at longer-term follow up. Finally, paired echocardiographic data analyses from COMPASSION showed statistically significant reductions in conduit mean gradient and conduit peak gradient at 1 year and through 5 years.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above.

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

In the COMPASSION Trial, patients demonstrated clinically acceptable rates of MACCE, which included all-cause mortality, myocardial infarction, reintervention, vascular injury resulting in the need for an unplanned vascular intervention, stroke and pulmonary embolism. Long-term follow-up showed acceptable rates of MACCE through 5 years. In addition, there were acceptably low incidences of endocarditis and valve dysfunction (defined as a non-hierarchical composite of all-cause mortality,

surgical pulmonary valve replacement, valve frame fracture, recurrent pulmonary stenosis, moderate/severe pulmonary regurgitation and reintervention) which were sustained through 5 years.

C. Benefit-Risk Conclusions

The probable benefits of the Pulmonic SAPIEN XT are based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefits include overall functional improvement of the pulmonary valve including reduction in mean and peak conduit gradients. The probable risks of the SAPIEN XT include procedural and long-term risks including vascular injury, RVOT conduit rupture, endocarditis, and valve dysfunction. Functional improvements may delay the need for reoperation and surgical replacement of the existing RVOT conduit. As such, the use of this device may reduce the frequency of reinterventions and diminish the total number of open heart surgeries required over a patient's lifetime, thus decreasing the risks associated with such operations.

In conclusion, given the available information above, the data support that for use in pediatric and adult patients with a dysfunctional, non-compliant, Right Ventricular Outflow Tract (RVOT) conduit or bioprosthetic valve in the pulmonic position, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Overall, data suggests that the SAPIEN XT used in the pulmonic position has a probable benefit of improving functional performance and may serve to reduce the frequency of re-operation on dysfunctional RVOT conduits.

XIV. CDRH DECISION

CDRH issued an approval order on February 29, 2016. The final conditions of approval cited in the approval order are described below. On the basis of the information reviewed, this firm has an acceptable GMP program

ODE Lead Post-Approval: Continued Follow-Up of the Premarket COMPASSION Cohort

The objective of this study is to evaluate longer-term safety and effectiveness of the device in the pulmonic position for all living subjects who were enrolled under the IDE. This study will be conducted as per the protocol (protocol J) dated November 3, 2010. Subject follow-up will continue based on the timelines outlined in the IDE protocol.

The study is a prospective, non-randomized, multi-center clinical trial designed to follow subjects from the IDE trial up to 5 years. Data will be collected per the protocol including freedom from device- or procedure-related death or reintervention, freedom from MACCE, functional improvement (decrease in pulmonary regurgitation, improvement in NYHA

functional class, freedom from recurrent pulmonary stenosis), procedural- and device-related adverse events, stent fracture, reintervention on the THV or conduit, and death.

OSB Lead PMA Post-Approval Study - New enrollment SAPIEN XT Pulmonic PAS:

The objective of this study is to evaluate longer-term safety and effectiveness of the SAPIEN XT THV in the pulmonic position for the intended patient population (especially pediatric) when used as indicated with all valve sizes. It is a single-arm, prospective, multicenter post-approval study using a performance goal based on the original COMPASSION trial.

The study patients are pediatric and adult patients with a dysfunctional, non-compliant right ventricular outflow tract (RVOT) conduit with a clinical indication for intervention and pulmonary regurgitation \geq moderate and/or mean RVOT gradient \geq 35 mmHg. The eligibility criteria will be consistent with the final FDA-approved IFU and labeling. A sample size of 162 subjects is required for the hypothesis test on the primary effectiveness endpoints with at least 80% of the power. A total of 191 patients will be enrolled at up to 10 sites in the US to account for loss to follow-up. The patients will be followed at hospital discharge, 30 days, 1 year and annually thereafter through 5 years.

The primary effectiveness endpoint is the freedom from device- or procedure-related death or reintervention at one year. The secondary effectiveness endpoints include 1) Improved THV hemodynamics at 1 year via transthoracic echocardiogram (TTE), 2) Improvement of \geq 1 NYHA functional class at 30 days and 1 year from baseline for patients with NYHA functional class \geq 2 at baseline, 3) freedom from recurrent pulmonary stenosis, defined as RVOT peak gradient $<$ 36 mmHg at one year as demonstrated via TTE for patients with stenosis at baseline (RVOT peak gradient \geq 36 mmHg at baseline), and 4) device success, which is defined as a composite of deployment of the valve to the target area, removal of the delivery catheter out of the body, and improvement in pulmonary regurgitation to mild or less per the earliest evaluable TTE. The secondary safety endpoint is the composite endpoint MACCE at 30 days and 1 year. MACCE is defined as a composite of death, myocardial infarction, reintervention, vascular injury resulting in the need for an unplanned vascular intervention, stroke and pulmonary embolism.

The acceptance criterion for the primary effectiveness endpoint is 11.1% (or 89.6% freedom from death and reintervention). If the lower 95% confidence limit for the freedom from the primary effectiveness endpoint at 1 year is greater than 89.6%, the acceptance criterion for the primary endpoint will have been met. Other endpoints and clinically relevant baseline and follow-up variables will be provided descriptively.

XV. 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.