SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Aortic or mitral 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 9600LDS2; Edwards Certitude delivery system, models 9600SDS20, 9600SDS23, 9600SDS26, and 9600SDS29; with crimp stopper and Qualcrimp crimping accessory; Edwards Certitude Introducer Sheath, models 9600IS18 and 9600IS21; and Edwards crimper, model 9600CR)
Device Procode:	NPT, NPU
Applicant Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P140031/S028
Date of FDA Notice of Approval:	June 5, 2017
Priority Review:	Granted priority review status on January 5, 2017 because the availability of the device is in the best interest of the patients

The original PMA of the Edwards SAPIEN 3 Transcatheter Heart Valve (THV), P140031, was approved on June 17, 2015, and the indication was later expanded in Panel Track PMA Supplement P140031/S010 on August 18, 2016, with a combined indication 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 intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator). The SSEDs to support the indication are available on the following FDA websites and are incorporated by reference herein:

- https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031b.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S010b.pdf

The current supplement was submitted to expand the indication for the SAPIEN 3 THV to include patients with a failed bioprosthetic heart valve in the aortic or mitral position (i.e., aortic valve-in-valve and mitral valve-in-valve, respectively).

II. INDICATIONS FOR USE

The Edwards SAPIEN 3 Transcatheter Heart Valve (THV), Model 9600TFX, and accessories are indicated for patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic or mitral valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the STS risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

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.

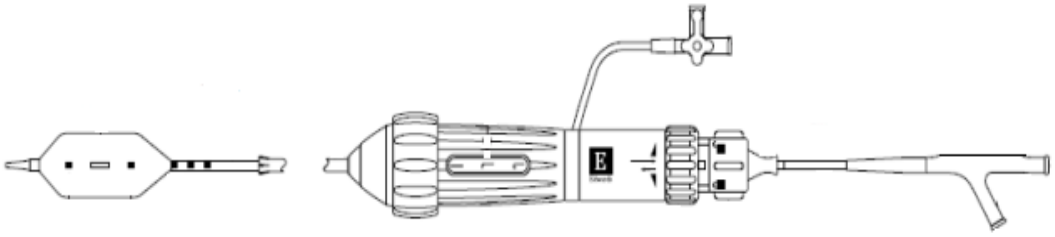
V. DEVICE DESCRIPTION

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. It is used when a long access route (e.g., transfemoral or subclavian) is planned.

Figure 2: Edwards Commander Delivery System

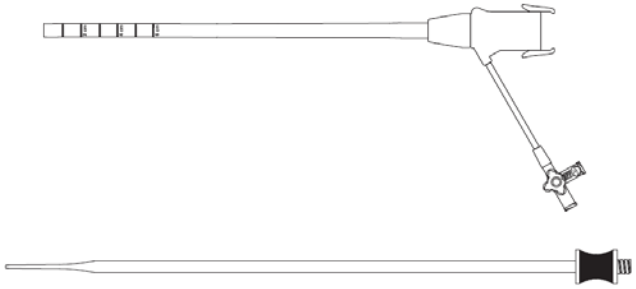


The Edwards Certitude Delivery System, as shown in Figure 3, includes a handle with a flex wheel for articulation of the balloon catheter, a loader, and extension tubing. It is used when a short access route (e.g., transapical or transaortic) is planned.

Figure 3: Edwards Certitude Delivery System

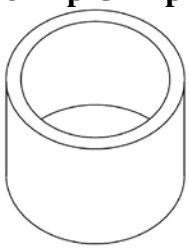
The Edwards Certitude introducer sheath, as shown in Figure 4, is intended for use with the Edwards Certitude Delivery System. It has a radiopaque marker for visualization of the sheath tip and non-radiopaque depth markings on the distal end. The proximal end of the introducer sheath includes a flush tube and three hemostasis valves.

Figure 4: Edwards Certitude Introducer Sheath



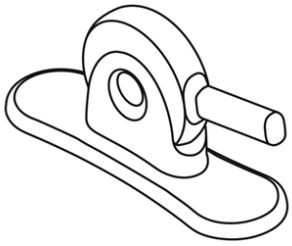
The Qualcrimp crimping accessory, shown in Figure 5, is placed around the Edwards SAPIEN 3 THV to protect the leaflets during the crimping process. It is manufactured of tubular polyester polyurethane foam and laminated cylindrically on both the inner and outer surfaces with a polyether urethane material.

Figure 5: Qualcrimp Crimping Accessory



The Edwards Crimper, as shown in Figure 6, 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 6: Edwards Crimper



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other alternatives for patients with a failing bioprosthetic valve in the aortic or mitral position, including percutaneous balloon valvuloplasty for temporary relief of stenosis, reoperative surgical replacement of the degenerated device, and palliative medical therapy without an obstruction-relieving procedure. 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 Edwards SAPIEN 3 THV has not been marketed in the United States or any foreign country for the aortic valve-in-valve or mitral valve-in-valve indication.

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. Those associated with access complications pertaining to standard cardiac catheterization, balloon valvuloplasty, the potential risks of conscious sedation and/or general anesthesia, and the use of angiography are as follows:

- 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, atrium, septum, myocardium or valvular structures that may require intervention
- Injury to the mitral valve
- Left ventricular outflow tract obstruction
- Pericardial effusion or cardiac tamponade
- Embolization including air, calcific valve material, or thrombus
- Infection including septicemia and endocarditis
- Heart failure
- Mediastinitis
- Mediastinal bleeding
- Myocardial infarction
- Renal insufficiency or renal failure
- Conduction system defect which may require a permanent pacemaker
- Arrhythmia
- Nonstructural dysfunction
- Retroperitoneal bleed
- Arteriovenous 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 re operation

For the specific adverse events that occurred in the real-world clinical practice, please see Section X.

IX. SUMMARY OF PRECLINICAL STUDIES

A summary of previously reported preclinical studies can be found in the SSED for the original PMA. Additional bench testing was conducted on the SAPIEN 3 valve-in-valve configurations, as summarized in Table 1.

Table 1. Summary of *In Vitro* Studies for SAPIEN 3 Valve-in-Valve Configurations

Test	Applicable Standard	Test Description	Results
SAPIEN 3 Valve-in-Valve Full Hydrodynamic Performance Testing	ISO 5840-3:2013	Hydrodynamic performance for the SAPIEN 3 THV in failed surgical bioprosthesis for steady forward flow, steady backflow leakage, and pulsatile testing for total regurgitation fraction and effective orifice area for aortic and mitral positions.	Pass

Test	Applicable Standard	Test Description	Results
SAPIEN 3 Valve-in-Valve Verification of Bernoulli Relationship	ISO 5840-3:2013	Hydrodynamic performance conducted to determine the coefficient 4 of the Bernoulli relationship remains the same for SAPIEN 3 THV in failed bioprosthesis configurations.	Pass
SAPIEN 3 Valve-in-Valve Flow Visualization	ISO 5840-3:2013	Quantitative flow visualization study conducted to determine velocity and shear flow fields in SAPIEN 3 THV in failed surgical bioprosthesis in the aortic position.	Pass
SAPIEN 3 Valve-in-Valve Resistance to Embolization	ISO 5840-3:2013	Resistance to embolization study conducted to determine the SAPIEN 3 THV in failed surgical bioprosthesis remains in the target implant site when subjected to 20 million cycles of accelerated wear testing for aortic and mitral positions.	Pass
SAPIEN 3 Valve-in-Valve Accelerated Wear Testing	ISO 5840-3:2013	Resistance to embolization study conducted to determine the SAPIEN 3 THV in failed surgical bioprosthesis remains in the target implant site when subjected to accelerated wear testing for aortic and mitral positions	Pass
SAPIEN 3 Valve-in-Valve Balloon Inflation and Burst Pressure in Constrained Configuration	N/A	Inflation and burst pressure testing conducted to determine the inflation and burst pressures of the SAPIEN 3 THV in a failed bioprosthesis configuration remains less than the rated burst pressure of the delivery system.	Pass
SAPIEN 3 Antegrade Position AWT (100M cycles)	ISO 5840-3:2013	Accelerated wear testing conducted for the SAPIEN 3 THV in surgical failed bioprosthesis in antegrade position for the mitral position.	Pass
SAPIEN 3 Positioning Guidance for Valve-in- Valve Deployment	N/A	Positioning guidance developed to provide optimal positioning for the SAPIEN 3 THV in a failed bioprosthesis configuration.	N/A

X. SUMMARY OF PRIMARY CLINICAL DATA

The applicant performed an analysis of the real-world off-label use data captured in the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry to establish a reasonable assurance of safety and effectiveness of transcatheter valve replacement with the Edwards SAPIEN 3

THV in patients with a failed surgical aortic or mitral bioprosthesis who are at high or greater surgical risk for reoperative aortic or mitral valve replacement. The data from the TVT Registry were the basis of the PMA supplemental approval decision. A summary of the clinical data is presented below.

A. Study Design

A database extract was performed on August 4, 2016, which yielded 314 patients that had been treated with an Edwards SAPIEN 3 THV placed in a failed surgical aortic bioprosthesis (i.e., aortic valve-in-valve) and 311 patients that had been treated with an Edwards SAPIEN XT THV (N = 241) or SAPIEN 3 THV (N = 70) placed in a failed surgical mitral bioprosthesis (i.e., mitral valve-in-valve). Patients who presented with an existing valve-in-valve that was failing (i.e., having more than 2 THVs) were excluded from the database extract. The SAPIEN XT THV was included in the database extract for the mitral valve-in-valve uses because there were fewer SAPIEN 3 THV cases in the registry due to its relatively shorter commercial use history and the SAPIEN XT THV data were considered to be generally applicable to the SAPIEN 3 THV due to their similarities in design. The aortic valve-in-valve patients were treated between July 23, 2015, and June 29, 2016, at 130 participating hospitals; the mitral valve-in-valve patients were treated at 112 participating hospitals between July 10, 2014, and June 27, 2016, for the SAPIEN XT THV and between June 23, 2015, and June 15th, 2016, for the SAPIEN 3 THV.

Adjudications were completed per the TVT Registry Coder's Data Dictionary by the Duke Clinical Research Institute (DCRI) for three adverse events: readmission for heart failure, stroke/transient ischemic attack (TIA), and aortic and mitral valve reinterventions.

1. Clinical Inclusion and Exclusion Criteria

Patients in the database extract received a commercially available SAPIEN 3 THV (for both aortic and mitral valve-in-valve) or SAPIEN XT THV (for mitral valve-in-valve only) for symptomatic heart disease associated with a failed (stenosed, insufficient, or combined) surgical bioprosthetic aortic or mitral valve. They were deemed to be at high or greater risk for open surgical therapy and were treated off-label based on the clinical judgement of their treating physicians.

2. Follow-up Schedule

All patients were followed post implantation according to their local standards of care. The TVT Registry collects follow-up data at discharge, 30 days, and 1 year.

3. Clinical Endpoints

Data entered into the TVT Registry were collected through standardized data collection forms. The endpoints analyzed in this application included: death, readmission for heart failure, stroke/TIA, valve reinterventions, key site reported adverse events, valve performance based on echocardiographic data, New York Heart Association (NYHA) classification, 6-minute or 5-meter walk test, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score. The analyses in the application focused on the discharge and 30-day time points.

B. Accountability of PMA Cohorts

At the time of database extract, of the 314 patients in the aortic valve-in-valve cohort, 299 patients were eligible for the 30-day visit, and 252 (84.3%) patients completed the visit within the 30-day follow-up window defined as the period between discharge + 1 day or 21 days post-procedure (whichever occurred first) and 75 days post-procedure; of the 311 patients (SAPIEN XT and SAPIEN 3 combined) in the mitral valve-in-valve cohort, 290 patients were eligible for the 30-day visit, and 244 (84.1%) patients completed the visit within the 30-day follow-up window. A detailed summary of the patient accountability at 30 days for the two PMA cohorts is shown in Table 2.

Table 2: PMA Cohorts Patient Accountability at 30-Day Follow-Up Visit

	Aortic Valve-in-Valve	Mitral Valve-in-Valve		
		SAPIEN XT	SAPIEN 3	All
Total patients	314	241	70	311
Non-eligible	15	15	6	21
-Death	11	15	4	19
-Withdrawal	0	0	0	0
-Lost to follow-up	1	0	2	2
-Visit not yet due	3	0	0	0
Eligible	299	226	64	290
-Follow-up visit completed	252 (84.3%)	196 (86.7%)	48 (75.0%)	244 (84.1%)
-Missed Visit	47 (15.7%)	30 (13.3%)	16 (25.0%)	46 (15.9%)

The “Attempted Implant” population consisted of all patients for whom the first vascular access was attempted. The “Valve Implant” population consisted of those patients for whom the valve implant procedure has started and a “No” was indicated for both “procedure aborted” and “conversion to open heart surgery.” The number of patients in each analysis population of the aortic valve-in-valve and mitral valve-in-valve cohorts is shown in Table 3.

Table 3: Analysis Populations

Analysis Population	Aortic Valve-in-Valve	Mitral Valve-in-Valve		
		SAPIEN XT	SAPIEN 3	All
All Enrolled population	314	241	70	311
Attempted Implant population	314	241	70	311
Valve Implant population	314	236	69	305

C. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of both the aortic and mitral valve-in-valve patients, as shown in Tables 4 and 5, present an elderly, multimorbid cohort of patients, consistent with the high operative risk of the populations.

Table 4: Patient Demographics and Baseline Characteristics - Aortic Valve-in-Valve (Attempted Implant Population)

Demographics and Baseline Characteristics	Summary Statistics*
Age – years	74.3 ± 12.10 (313)
Male sex	188/314
Society of Thoracic Surgeons (STS) score	9.0 ± 8.0 (304)
New York Heart Association (NYHA) class	
I/II	45/312 (14.4%)
III/IV	267/312 (85.6%)
Previous myocardial infarction	62/313 (19.8%)
Previous intervention	
Coronary artery bypass grafting (CABG)	119/314 (37.9%)
Percutaneous coronary intervention (PCI)	56/314 (17.8%)
Prior aortic valvuloplasty	10/306 (3.3%)
Cerebrovascular accident (CVA)	46/313 (14.7%)
Peripheral vascular disease	79/314 (25.2%)
Atrial fibrillation	126/314 (40.1%)
Permanent pacemaker	53/314 (16.9%)
Porcelain aorta	19/314 (6.1%)
Hostile chest	58/314 (18.5%)
Echocardiographic findings (Valve Implant Population)	
Valve area - cm^2	0.8 ± 0.4 (230)
Mean aortic-valve gradient – mmHg	39.3 ± 15.8 (251)
Mean left ventricular ejection fraction (LVEF)%	52.2 ± 13.1 (308)
Moderate or severe aortic regurgitation	168/310 (54.2%)
Moderate or severe mitral regurgitation	126/261 (48.3%)

*Continuous measures - Mean ± SD (Total no.); Categorical measures - n. / Total no. (%)

Table 5: Patient Demographics and Baseline Characteristics - Mitral Valve-in-Valve (Attempted Implant Population)

Demographics and Baseline Characteristics	Summary Statistics*		
	SAPIEN XT	SAPIEN 3	All
Age – years	73.9 ± 12.4 (241)	71.5 ± 15.0 (70)	73.4 ± 13.1 (311)
Male sex	88/241 (36.5%)	32/70 (45.7%)	120/311 (38.6%)
Society of Thoracic Surgeons (STS) score	13.2 ± 9.1 (237)	12.2 ± 8.7 (65)	13.0 ± 8.98 (302)
New York Heart Association (NYHA) class			
I/II	30/238 (12.6%)	3/70 (4.3%)	33/308 (10.7%)
III/IV	208/238 (87.4%)	67/70 (95.7%)	275/308 (89.3%)
Previous myocardial infarction	47/239 (19.7%)	18/70 (25.7%)	65/309 (21.0%)
Previous intervention			
Coronary artery bypass grafting (CABG)	93/236 (39.4%)	28/69 (40.6%)	121/305 (39.7%)
Percutaneous coronary intervention (PCI)	32/238 (13.4%)	9/69 (13.0%)	41/307 (13.4%)
Cerebrovascular accident (CVA)	45/241 (18.7%)	15/70 (21.4%)	60/311 (19.3%)
Peripheral vascular disease	42/239 (17.6%)	6/70 (8.6%)	48/309 (15.5%)
Atrial fibrillation/flutter	155/241 (64.3%)	50/70 (71.4%)	205/311 (65.9%)
Permanent pacemaker	74/240 (30.8%)	20/69 (29.0%)	94/309 (30.4%)
Porcelain aorta	6/240 (2.5%)	1/69 (1.4%)	7/309 (2.3%)
Hostile chest	41/241 (17.0%)	6/70 (8.6%)	47/311 (15.1%)
Echocardiographic findings (Valve Implant Population)			
Mitral valve area - cm^2	1.5 ± 0.9 (153)	1.4 ± 1.0 (46)	1.5 ± 0.88 (199)
Mean mitral-valve gradient - mmHg	12.7 ± 5.5 (215)	13.7 ± 6.2 (65)	12.9 ± 5.65 (280)
Mean left ventricular ejection fraction (LVEF), %	54.4 ± 11.7 (230)	53.8 ± 13.9 (67)	54.3 ± 12.2 (297)
Moderate or severe aortic regurgitation	35/231 (15.2%)	7/67 (10.5%)	42/298 (14.1%)
Moderate or severe mitral regurgitation	149/233 (63.9%)	39/68 (57.4%)	188/301 (62.5%)

*Continuous measures - Mean ± SD (Total no.); categorical measures - n. / Total no. (%). The total no. only counted the patients with valid values.

D. Safety and Effectiveness Results

D.1. Aortic Valve-in-Valve

1. Safety Endpoints

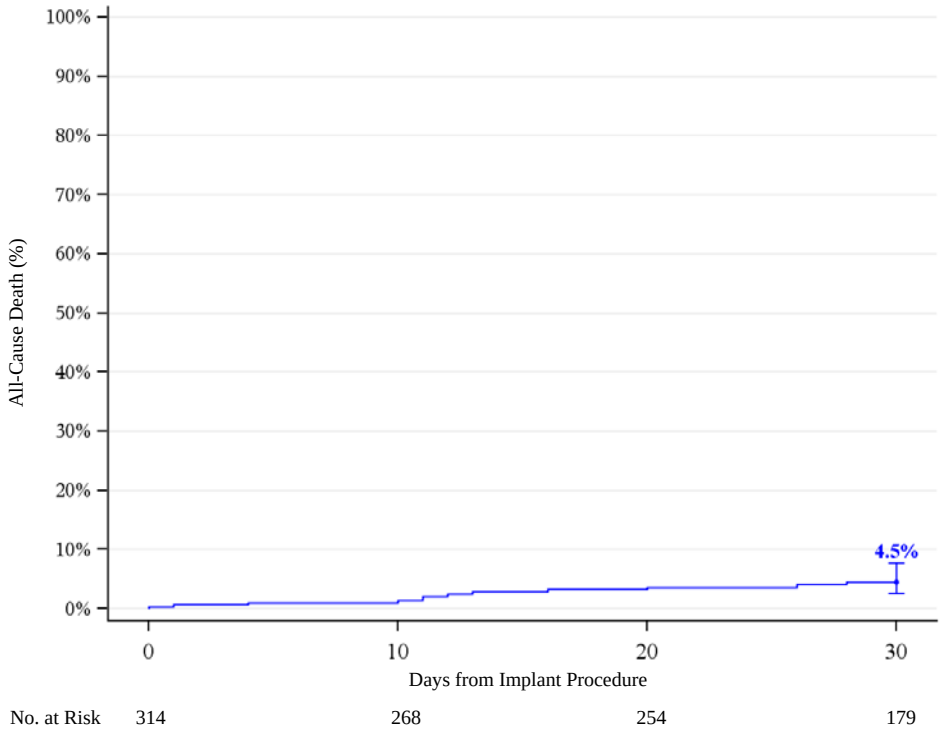
The mortality rates at discharge and 30 days and the Kaplan-Meier curve for all-cause mortality for the aortic valve-in-valve cohort are shown in Table 6 and Figure 7, respectively. There were a total of 12 deaths reported at 30 days.

Table 6: Death Rate - Aortic Valve-in-Valve (Attempted Implant Population)

	Discharge*	30 Days†
All-cause death	2.5% (8)	4.5% (12)
Cardiac death	1.3% (4)	2.2% (6)

*Observed rate - % (n)
†Kaplan-Meier estimate - % (n)

Figure 7: All-Cause Death Rate - Aortic Valve-in-Valve (Attempted Implant Population)



The DCRI adjudicated events, including all strokes/TIAs and aortic valve reinterventions at discharge and 30 days for the aortic valve-in-valve cohort, are shown in Table 7.

Table 7: Duke Clinical Research Institute Adjudicated Events - Aortic Valve-in-Valve (Attempted Implant Population)

Events	Discharge*	30 Days†
All stroke	1.0% (3, 3)	1.0% (3, 3)
Ischemic stroke	1.0% (3, 3)	1.0% (3, 3)
Hemorrhagic stroke	0.0% (0, 0)	0.0% (0, 0)
Transient ischemic attack (TIA)	0.0% (0, 0)	0.0% (0, 0)
Aortic valve reintervention	0.3% (1, 1)	0.3% (1, 1)

*Observed rate - % (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)

2. Site Reported Adverse Events

The site reported adverse events at discharge and 30 days for the aortic valve-in-valve cohort is shown in Table 8.

Table 8: Site Reported Adverse Events - Aortic Valve-in-Valve (Attempted Implant Population)

Events	Discharge*	30 Days†
Non-valve related readmission	N/A	5.9% (15, 15)
Minor vascular complication	3.8% (12, 12)	4.3% (13, 13)
Conduction/native pacer disturbance requiring pacer	2.9% (9, 9)	3.0% (9, 9)
Hematoma at access site	2.9% (9, 9)	2.9% (9, 9)
Atrial fibrillation	2.5% (8, 8)	2.6% (8, 8)
Bleeding at access site	2.5% (8, 8)	2.5% (8, 8)
Cardiac arrest	2.5% (8, 8)	2.5% (8, 8)
Unplanned vascular surgery or intervention	1.6% (5, 5)	2.0% (7, 6)
Percutaneous coronary intervention (PCI)	1.3% (4, 4)	1.7% (5, 5)
Other bleed	1.3% (4, 4)	1.3% (4, 4)
Coronary compression or obstruction	1.0% (3, 3)	1.0% (3, 3)
Hemorrhagic stroke	0.6% (2, 2)	1.1% (3, 3)
Life threatening bleeding	N/A	1.1% (3, 3)
Unplanned other cardiac surgery or intervention	1.0% (3, 3)	1.0% (3, 3)
Major bleeding event	N/A	0.8% (2, 2)
Major vascular complication	0.6% (2, 2)	0.6% (3, 2)
Myocardial infarction	0.3% (1, 1)	0.7% (2, 2)
New requirement for dialysis	0.6% (2, 2)	0.8% (2, 2)
Other device related event	0.6% (2, 2)	0.6% (2, 2)
Aortic valve re-intervention	0.0% (0, 0)	0.4% (1, 1)
Conduction/native pacer disturbance requiring implantable cardioverter defibrillator (ICD)	0.3% (1, 1)	0.3% (1, 1)

Events	Discharge*	30 Days†
Device migration	0.3% (1, 1)	0.3% (1, 1)
Gastrointestinal bleeding (GI) bleed	0.3% (1, 1)	0.3% (1, 1)
Transapical related event	0.3% (1, 1)	0.3% (1, 1)
Valve related readmission	N/A	0.4% (1, 1)
Device thrombosis	0.0% (0, 0)	0.0% (0, 0)

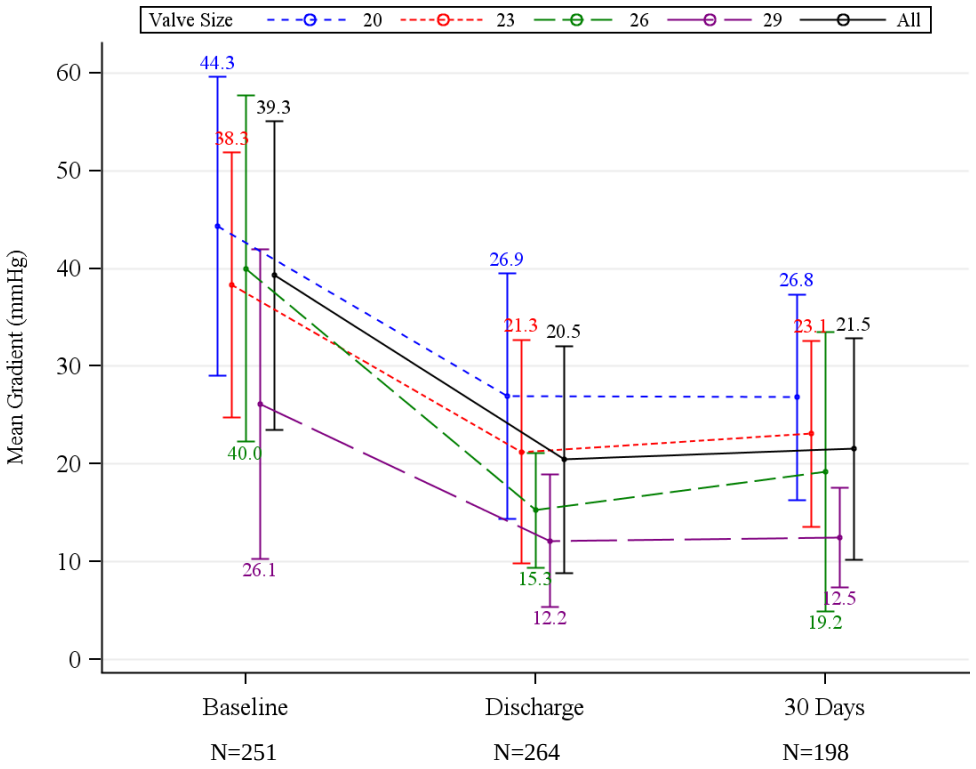
*Observed rate - % (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)

3. Effectiveness Endpoints

Valve Performance

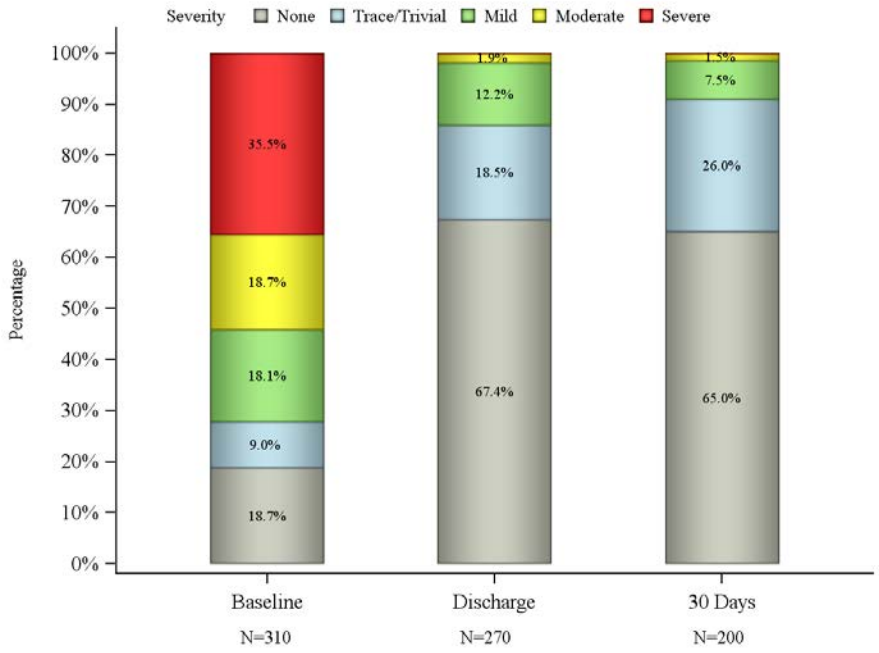
The aortic valve-in-valve echocardiographic performance data are summarized in Figures 8-10. The mean gradients improved from 39.3 ± 15.8 mmHg at baseline to 21.5 ± 11.3 mmHg at 30 days. Moderate/severe aortic regurgitation was observed in 54.2% of the patients at baseline, which decreased to 1.5% of the patients at 30 days.

Figure 8: Mean Gradient by Visit - Aortic Valve-in-Valve (Valve Implant Population)



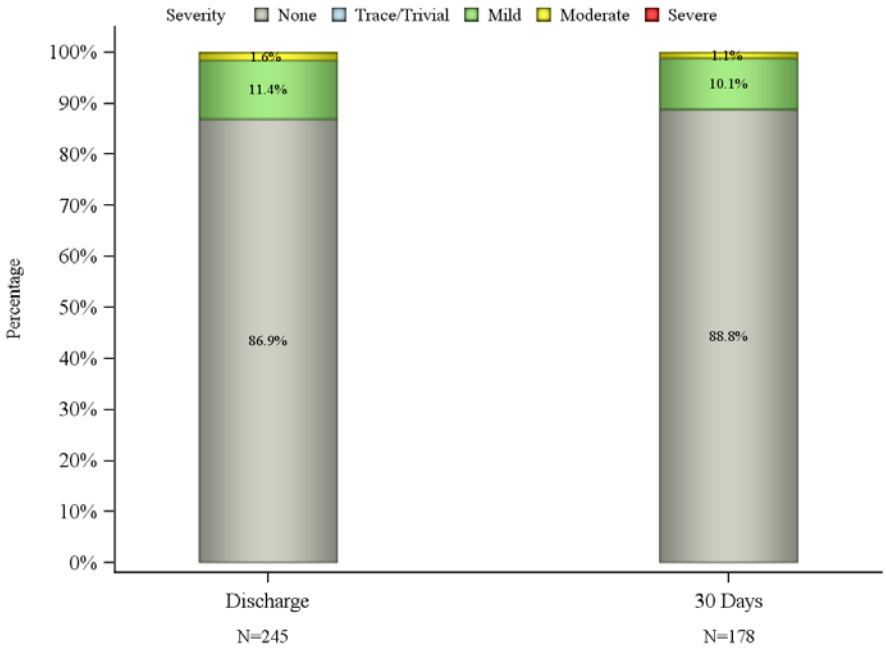
Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

Figure 9: Aortic Regurgitation by Visit - Aortic Valve-in-Valve (Valve Implant Population)



Note: The total number of patients at each time point only counted the patients with valid values.

Figure 10: Paravalvular Regurgitation by Visit - Aortic Valve-in-Valve (Valve Implant Population)

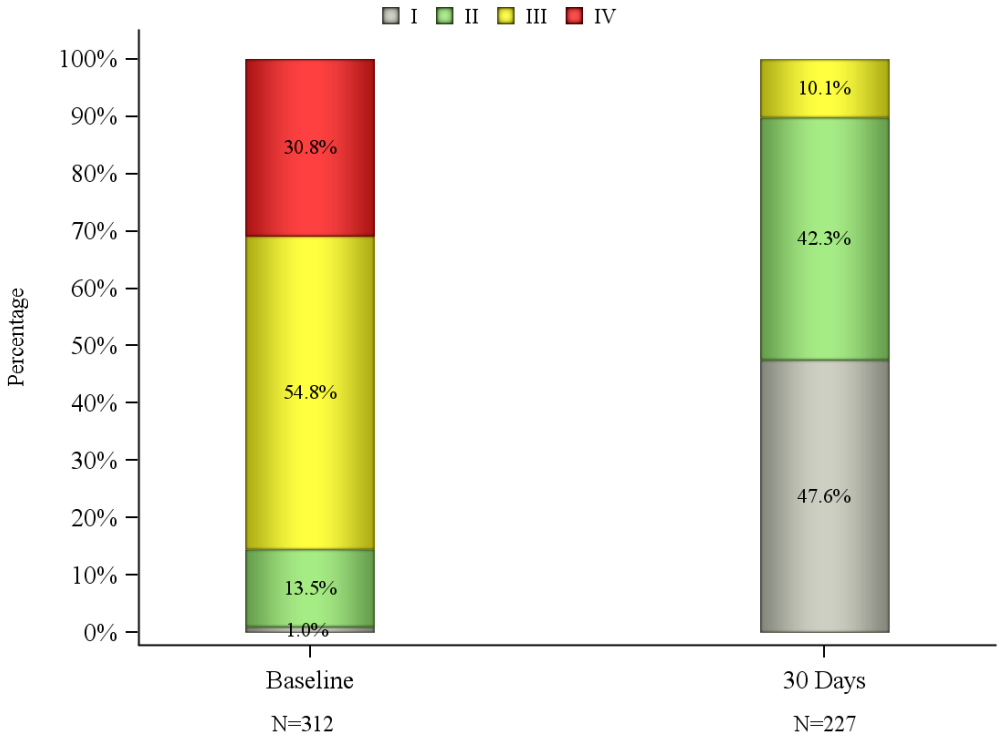


Note: The total number of patients at each time point only counted the patients with valid values.

NYHA Class

The NYHA class distributions at baseline and the 30-day visit and the NYHA class changes from baseline to the 30-day visit are shown in Figure 11 and Table 9, respectively. The majority (85.4%) of the patients had an improved NYHA class at the 30-day visit.

Figure 11: NYHA Functional Class - Aortic Valve-in-Valve (Valve Implant Population)



Note: The total number of patients at each time point only counted the patients with valid values.

Table 9: NYHA Class Change - Aortic Valve-in-Valve (Valve Implant Population)

	NYHA Class Change*		
	Improved	**Same**	**Worsened**
Baseline to 30-day visit	193/226 (85.4%)	31/226 (13.7%)	2/226 (0.9%)

*n/Total no. (%); the total no. only counted the patients with valid values.

Five-Meter Walk Test

The results of the five-meter walk test are summarized in Table 10.

Table 10: Five-Meter Walk Test - Aortic Valve-in-Valve (Valve Implant Population)

Visit*	Five Meter Walk Time (seconds)†
Baseline	7.6 ± 3.9 (209)
30-day visit	5.9 ± 2.4 (68)
Change from baseline to 30 day visit	-1.4 ± 2.9 (51)

*There were up to 3 five-meter walk tests for each patient at each visit, and the results were averaged.
†Mean ± SD (Total no.). The total number of patients at each time point only counted the patients with valid values.

Length of Stay

The mean index hospitalization stay was 4.9 days, which included an average of 1.8 days in the intensive care unit (ICU), as summarized in Table 11.

Table 11: Index Hospitalization Stay - Aortic Valve-in-Valve (Attempted Implant Population)

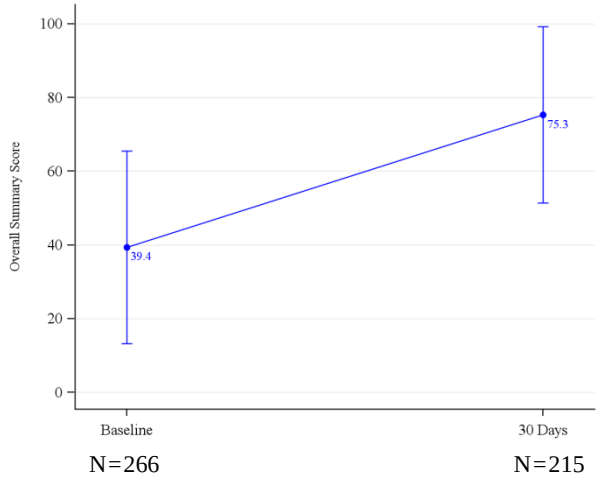
	Length (days)*
Index Hospitalization Stay	4.9 ± 3.9 (314)
Intensive Care Stay	1.8 ± 2.6 (311)

*Mean ± SD (Total no.).

Quality of Life (QoL)

The QoL at baseline and 30 days as measured by the KCCQ clinical summary score is shown in Figure 12. The mean KCCQ summary score improved from 39.4 at baseline to 75.3 at 30 days.

Figure 12: KCCQ Overall Summary Score - Aortic Valve-in-Valve (Valve Implant Population)



Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

4. Procedural Information

The procedure information is presented in Table 12. The most common delivery approach for the aortic valve-in-valve implantation was the transfemoral approach, which was used in 93.0% (292/314) of cases, followed by the transapical approach in 4.1% (13/314) of cases, and other alternative approaches (transaortic, subclavian, and other) in 2.9% (9/314) of cases. There were no aborted procedures or conversions to open heart surgery. The overall device success rate was 88.9% (272/306), which was defined as the following:

- Successful vascular access, delivery, and deployment of the device and successful retrieval of the delivery system, and
- Correct position of the device in the proper anatomical location, and
- Intended performance of the prosthetic heart valve (aortic valve area >1.2 cm^2 and mean aortic valve gradient < 20 mm Hg or peak velocity < 3 m/s, without moderate or severe prosthetic valve regurgitation), and
- Only one valve implanted in the proper anatomical location.

Table 12: Procedural Data Summary - Aortic Valve-in-Valve (Attempted Implant Population)

Procedural Data	Summary Statistics*
Operator Reason for Procedure	
Inoperable/extreme risk	80/313 (25.6%)
High risk	219/313 (70.0%)
Intermediate risk	10/313 (3.2%)
Low risk	4/313 (1.3%)
Implant Approach	
Transfemoral	292/314 (93.0%)
Transapical	13/314 (4.1%)
Transaortic	1/314 (0.3%)
Subclavian/axillary	6/314 (1.9%)
Other†	2/314 (0.6%)
Prior Valve Type	
Bioprosthetic stented	159/308 (51.6%)
Bioprosthetic stentless	79/308 (25.6%)
Procedure Status	
Elective	231/314 (73.6%)
Urgent	74/314 (23.6%)
Emergency	8/314 (2.5%)
Salvage	1/314 (0.3%)
Valve Size	
20 mm	83/314 (26.4%)

Procedural Data	Summary Statistics*
23 mm	130/314 (41.4%)
26 mm	57/314 (18.2%)
29 mm	44/314 (14.0%)
Primary Procedure Indication	
Aortic stenosis (Primary)	95/313 (30.4%)
Aortic insufficiency (Primary)	19/313 (6.1%)
Mixed aortic stenosis/aortic insufficiency	10/313 (3.2%)
Failed bioprosthetic valve	189/313 (60.4%)
Cardiopulmonary Bypass (CPB)	5/314 (1.6%)
CPB status	
Elective	4/5 (80.0%)
Emergent	1/5 (20.0%)
CPB time (min)	90.5 ± 140.9 (4)
Type of Anesthesia	
General anesthesia	240/314 (76.4%)
Moderate sedation	72/314 (22.9%)
Epidural	0/314 (0.0%)
Combination	2/314 (0.6%)
Total procedure time (min)	110.7 ± 63.0 (314)
Fluoroscopy time (min)	21.2 ± 16.1 (304)
Device success	272/306 (88.9%)
Procedure aborted	0/314 (0.0%)
Conversion to open heart surgery	0/314 (0.0%)
Mechanical assist device in place at start of procedure	5/313 (1.6%)
Intra-aortic balloon pump (IABP)	2/5 (40.0%)
Catheter based assist device	3/5 (60.0%)

*Categorical measures – no./Total no. (%); continuous measures - mean ± SD (Total no.). The total no. only counted the patients with valid values at the time point.
†The data collection form was changed in February 2013 to specify non-transfemoral (non-TF), non-transapical (non-TA) approaches rather than "other;" hence, "other" likely included the non-TF and non-TA approaches.

D.2. Mitral Valve-in-Valve

1. Safety Endpoints

The mortality rates at discharge and 30 days and the Kaplan-Meier curve for all-cause mortality for the mitral valve-in-valve cohort are shown in Table 13 and Figure 13, respectively. There were 16 reported deaths in the SAPIEN XT patients and 4 in the SAPIEN 3 patients at 30 days.

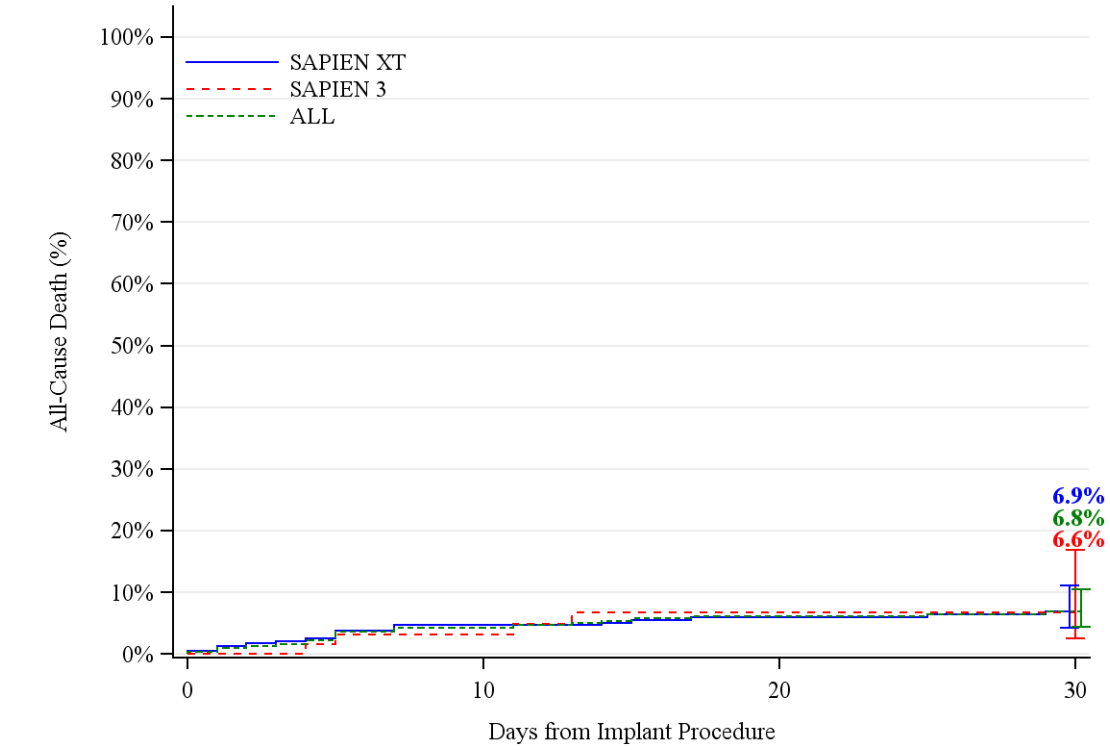
Table 13: Death Rate – Mitral Valve-in-Valve (Attempted Implant Population)

Event	Discharge*			30 Days†		
	SAPIEN XT	SAPIEN 3	All	SAPIEN XT	SAPIEN 3	All
All-cause death	5.0% (12)	5.7% (4)	5.1% (16)	6.9% (16)	6.6% (4)	6.8 % (20)
Cardiac death	3.7% (9)	4.3% (3)	3.9% (12)	4.2% (10)	4.9% (3)	4.3 % (13)

*Observed rate - % (n)

†Kaplan-Meier estimate - % (n)

Figure 13: All-Cause Death Rate – Mitral Valve-in-Valve (Attempted Implant Population)



No. at Risk				
SAPIEN XT	241	216	209	186
SAPIEN 3	70	56	52	45
ALL	311	272	261	231

The DCRI-adjudicated events, including all strokes/TIAs, heart failure readmissions, and mitral valve reinterventions at discharge and 30 days, for the mitral valve-in-valve cohort are shown in Table 14.

Table 14: Duke Clinical Research Institute Adjudicated Events - Mitral Valve-in-Valve (Attempted Implant Population)

Events	Discharge*			30 Day†		
	SAPIEN XT	SAPIEN 3	All	SAPIEN XT	SAPIEN 3	All
All stroke	0.4% (1, 1)	1.4% (1, 1)	0.6% (2, 2)	0.4% (1, 1)	1.5% (1, 1)	0.7% (2, 2)
Ischemic stroke	0.4% (1, 1)	1.4% (1, 1)	0.6% (2, 2)	0.4% (1, 1)	1.5% (1, 1)	0.7% (2, 2)
Hemorrhagic stroke	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Transient ischemic attack (TIA)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Readmission - heart failure	N/A	N/A	N/A	1.0% (2, 2)	0.0% (0, 0)	0.8% (2, 2)
Mitral valve reintervention	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.5% (1, 1)	0.0% (0, 0)	0.4% (1, 1)

*Observed rate - % (no. of events, no. of subjects with the event)

†Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)

2. Site Reported Adverse Events

The site reported adverse events at discharge and 30 days for the mitral valve-in-valve cohort are shown in Table 15.

Table 15: Site Reported Adverse Events - Mitral Valve-in-Valve (Attempted Implant Population)

Events	Discharge*			30 Day†		
	SAPIEN XT	SAPIEN 3	All	SAPIEN XT	SAPIEN 3	All
Other bleed	5.4% (13, 13)	4.3% (3, 3)	5.1% (16, 16)	6.1% (14, 14)	4.4% (3, 3)	5.8% (17, 17)
Readmission - not cardiac	N/A	N/A	N/A	5.8% (12, 12)	0.0% (0, 0)	4.6% (12, 12)
Atrial septal defect closure following transseptal catheterization	4.6% (11, 11)	5.7% (4, 4)	4.8% (15, 15)	4.6% (11, 11)	5.7% (4, 4)	4.9% (15, 15)
Cardiac arrest	4.1% (10, 10)	2.9% (2, 2)	3.9% (12, 12)	4.2% (10, 10)	3.2% (2, 2)	4.0% (12, 12)
Unplanned other cardiac surgery or intervention	3.3% (8, 8)	0.0% (0, 0)	2.6% (8, 8)	3.8% (9, 9)	0.0% (0, 0)	3.0% (9, 9)
Atrial fibrillation	3.3% (8, 8)	1.4% (1, 1)	2.9% (9, 9)	3.4% (8, 8)	1.5% (1, 1)	2.9% (9, 9)
New requirement for dialysis	2.9% (7, 7)	1.4% (1, 1)	2.6% (8, 8)	3.0% (7, 7)	1.6% (1, 1)	2.7% (8, 8)
Bleeding at access site	2.5% (6, 6)	1.4% (1, 1)	2.3% (7, 7)	2.5% (6, 6)	1.4% (1, 1)	2.3% (7, 7)

Events	Discharge*			30 Day†		
	SAPIEN XT	SAPIEN 3	All	SAPIEN XT	SAPIEN 3	All
Unplanned vascular surgery or intervention	2.5% (6, 6)	2.9% (2, 2)	2.6% (8, 8)	2.5% (6, 6)	3.2% (2, 2)	2.6% (8, 8)
Perforation with or w/o tamponade	2.1% (5, 5)	0.0% (0, 0)	1.6% (5, 5)	2.1% (5, 5)	0.0% (0, 0)	1.6% (5, 5)
Hematoma at access site	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)	1.3% (3, 3)	0.0% (0, 0)	1.0% (3, 3)
Minor vascular complication	1.2% (3, 3)	1.4% (1, 1)	1.3% (4, 4)	1.2% (3, 3)	1.7% (1, 1)	1.3% (4, 4)
Transapical related event	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)
Transseptal related event	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)
Gastrointestinal bleed	0.8% (2, 2)	1.4% (1, 1)	1.0% (3, 3)	0.9% (2, 2)	1.4% (1, 1)	1.1% (3, 3)
Major vascular complication	0.8% (2, 2)	0.0% (0, 0)	0.6% (2, 2)	0.8% (2, 2)	0.0% (0, 0)	0.6% (2, 2)
Readmission - cardiac	N/A	N/A	N/A	0.9% (2, 2)	0.0% (0, 0)	0.8% (2, 2)
Device embolization	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.5% (1, 1)	0.0% (0, 0)	0.4% (1, 1)
Device migration	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.5% (1, 1)	1.4% (1, 1)	0.7% (2, 2)
Device recapture or retrieval	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.5% (1, 1)	1.4% (1, 1)	0.7% (2, 2)
Genitourinary bleed	0.4% (1, 1)	0.0% (0, 0)	0.3% (1, 1)	0.4% (1, 1)	0.0% (0, 0)	0.3% (1, 1)
Major bleeding event	N/A	N/A	N/A	0.5% (1, 1)	0.0% (0, 0)	0.4% (1, 1)
Non-valve related readmission	N/A	N/A	N/A	0.5% (1, 1)	0.0% (0, 0)	0.4% (1, 1)
Conduction/native pacer disturbance requiring pacer	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.0% (0, 0)	1.5% (1, 1)	0.3% (1, 1)
Device thrombosis	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Endocarditis	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Life threatening bleeding	N/A	N/A	N/A	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Myocardial infarction	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)
Other device related event	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)
Transient ischemic attack	0.4% (1, 1)	0.0% (0, 0)	0.3% (1, 1)	0.4% (1, 1)	0.0% (0, 0)	0.3% (1, 1)
Ischemic stroke	0.4% (1, 1)	1.4% (1, 1)	0.6% (2, 2)	0.4% (1, 1)	1.5% (1, 1)	0.7% (2, 2)

Events	Discharge*			30 Day†		
	SAPIEN XT	SAPIEN 3	All	SAPIEN XT	SAPIEN 3	All
Readmission - heart failure	N/A	N/A	N/A	1.0% (2, 2)	3.8% (2, 2)	1.6% (4, 4)

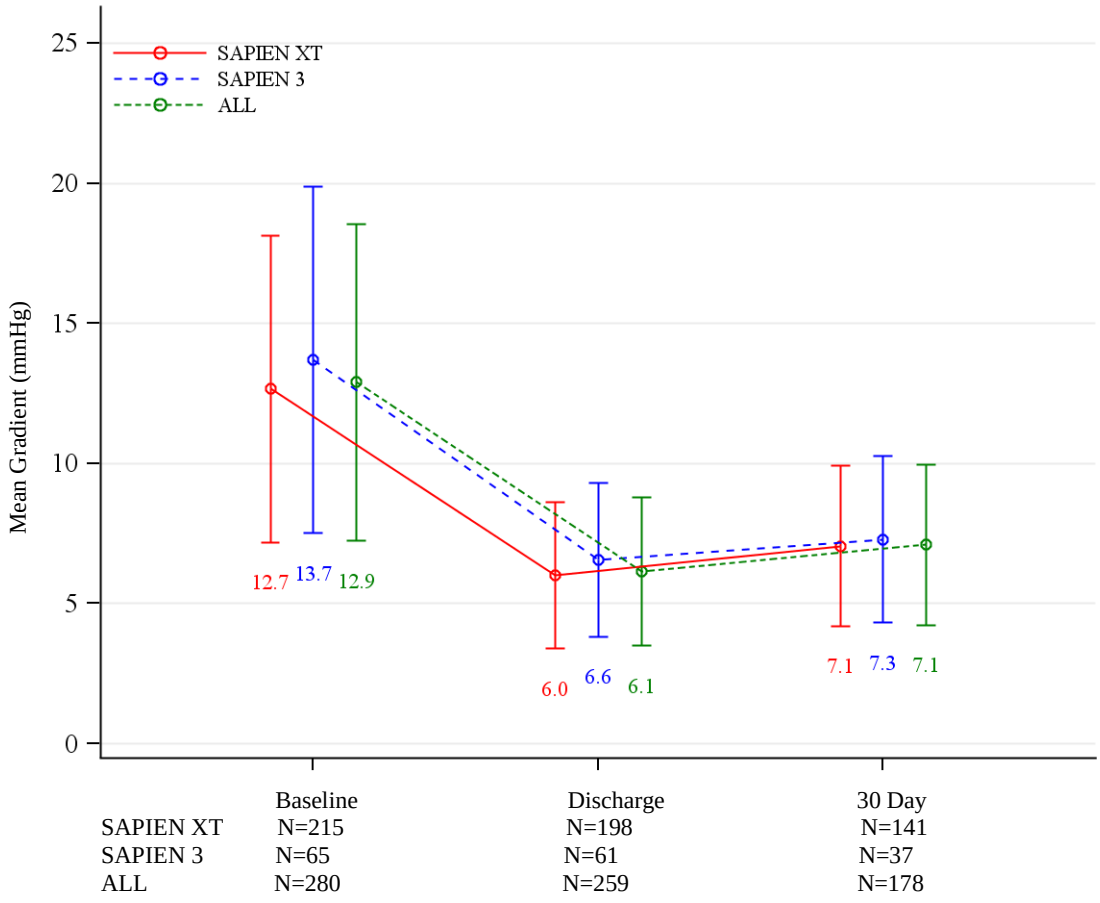
*Observed rate,% (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate,% (no. of events, no. of subjects with the event)

3. Effectiveness Endpoints

Valve Performance

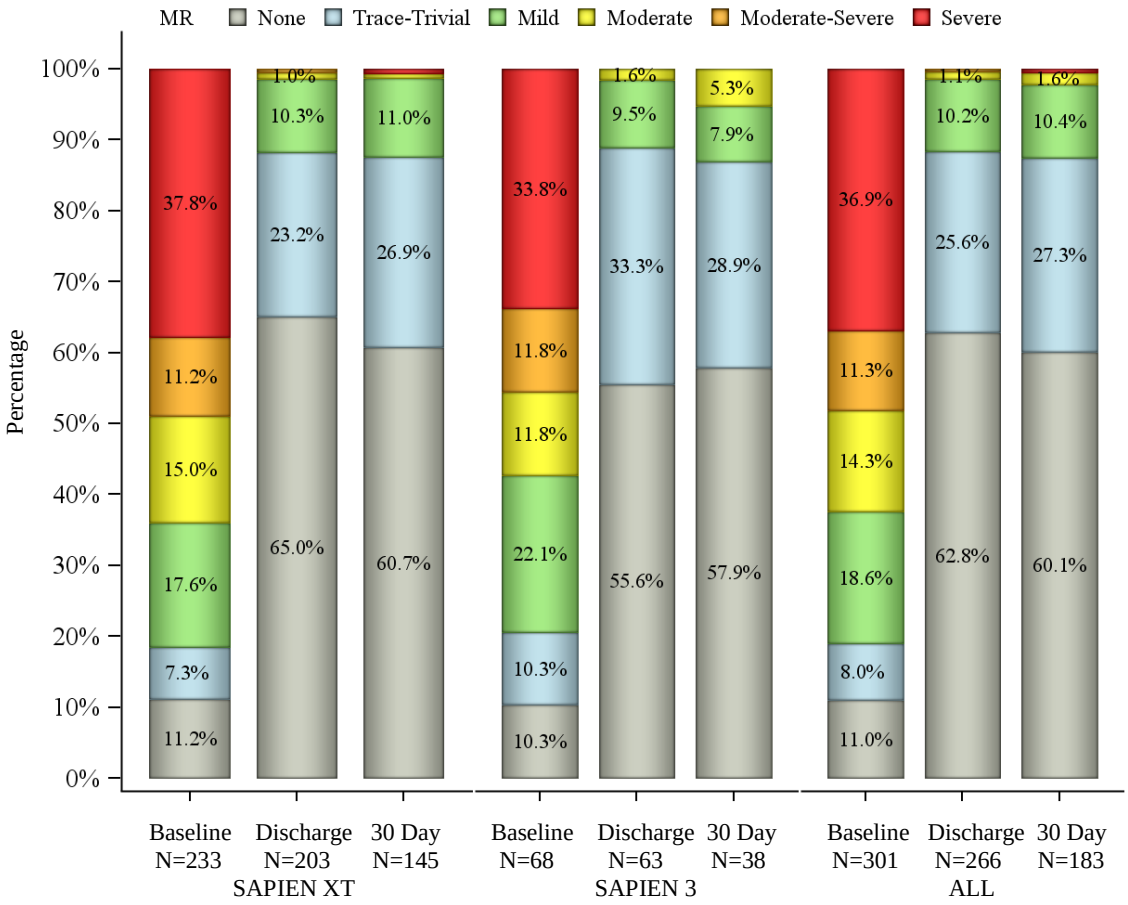
The mitral valve-in-valve echocardiographic performance data are summarized in Figures 14-16. The mean gradients improved from 12.9 mmHg at baseline to 7.1 mmHg at 30 days. Moderate/severe mitral regurgitation was observed in 62.5% of the patients at baseline, which decreased to 2.2% of the patients at 30 days.

Figure 14: Mean Gradient by Visit - Mitral Valve-in-Valve (Valve Implant Population)



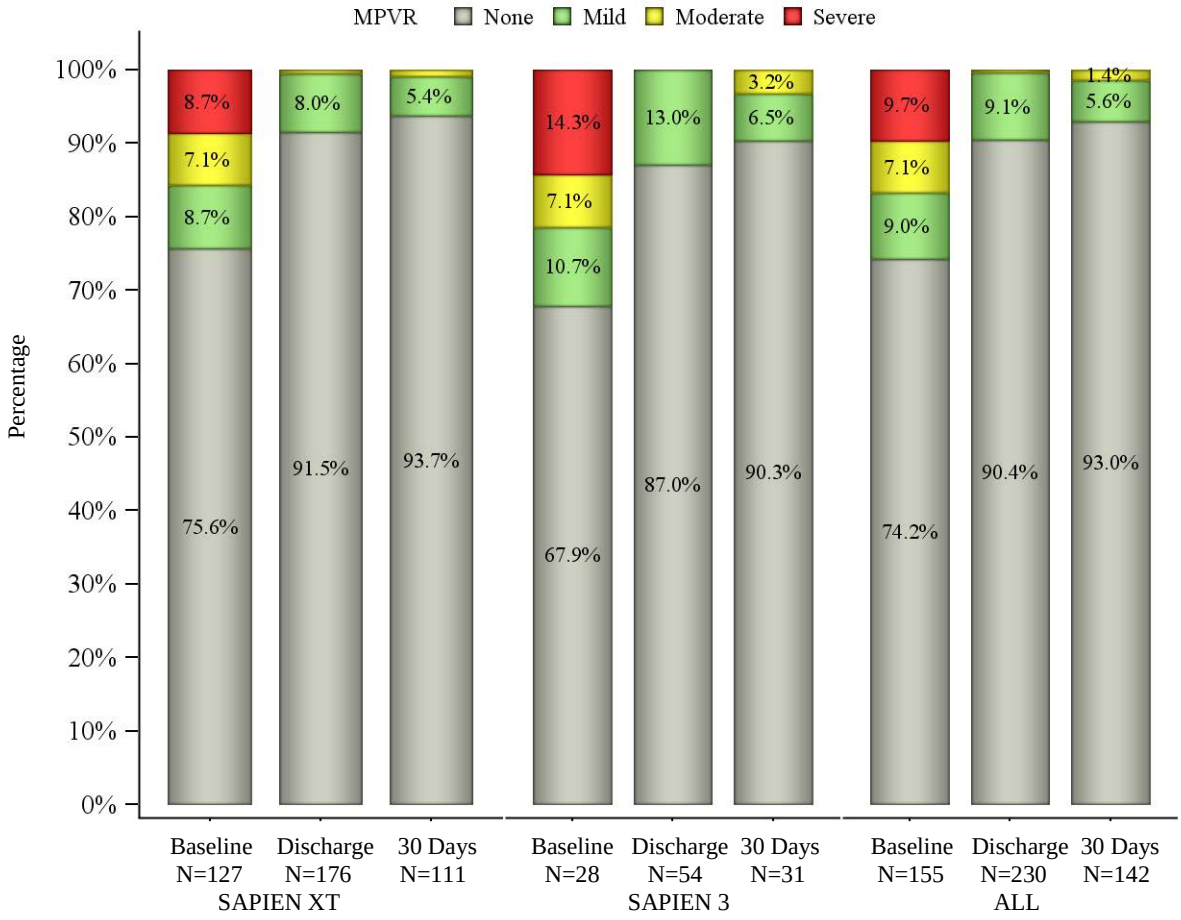
Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

Figure 15: Mitral Regurgitation by Visit - Mitral Valve-in-Valve (Valve Implant Population)



Note: Values that are < 1.0% are not labeled in the bar chart. The total number of patients at each time point only counted the patients with valid values.

Figure 16: Paravalvular Regurgitation by Visit - Mitral Valve-in-Valve (Valve Implant Population)

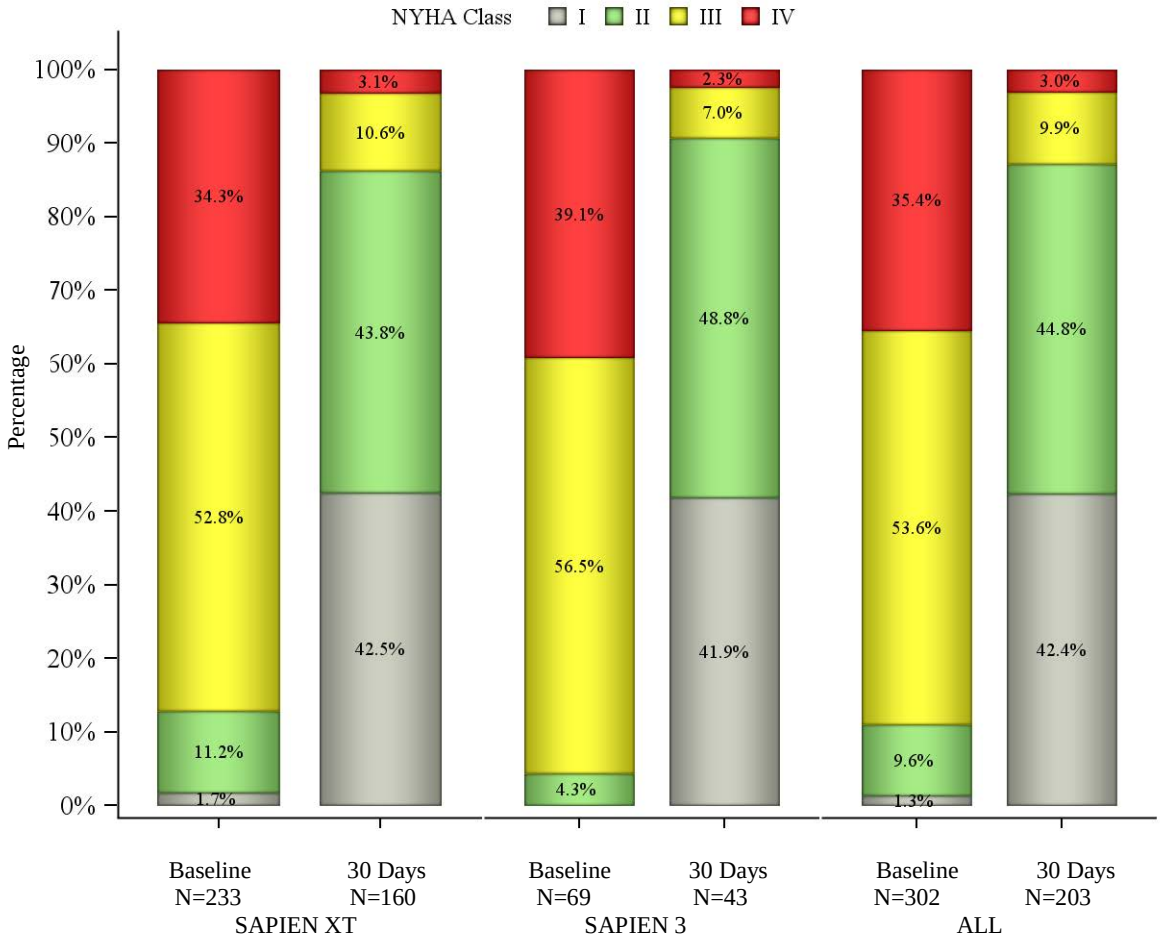


Note: Values that are < 1.0% are not labeled in the bar chart. The total number of patients at each time point only counted the patients with valid values.

NYHA Class

The NYHA class distributions at baseline and the 30-day visit and the NYHA class changes from baseline to the 30-day visit are shown in Figure 17 and Table 16, respectively. The majority (85.6%) of the patients had an improved NYHA class at the 30-day visit.

Figure 17: NYHA Functional Class - Mitral Valve-in-Valve (Valve Implant Population)



Note: The total number of patients at each time point only counted the patients with valid values.

Table 16: NYHA Class Change - Mitral Valve-in-Valve (Valve Implant Population)

		NYHA Class Change*		
		Improved	**Same**	**Worsened**
Baseline to 30-day visit	SAPIEN XT	133/159 (83.6%)	24/159 (15.1%)	2/159 (1.3%)
	SAPIEN 3	40/43 (93.0%)	3/43 (7.0%)	0/43 (0.0%)
	All	173/202 (85.6%)	27/202 (13.4%)	2/202 (1.0%)

*n/Total no. (%); the total no. only counted the patients with valid values.

Six-Minute Walk Test (6MWT)

The results of the 6MWT are summarized in Table 17.

Table 17: Six-Minute Walk Test - Mitral Valve-in-Valve (Valve Implant Population)

Visit	6-Minute Walk Distance (feet)*		
	SAPIEN XT	SAPIEN 3	All
Baseline	240.5 ± 366.2 (77)	375.6 ± 370.4 (32)	280.2 ± 370.9 (109)
30-day visit	768.7 ± 480.6 (34)	977.5 ± 597.4 (8)	808.5 ± 503.7 (42)
Change from baseline to 30 days	479.0 ± 471.3 (20)	457.6 ± 348.1 (5)	474.7 ± 442.9 (25)

*Mean ± SD (Total no.). The total number of patients at each time point only counted the patients with valid values. The 6-minute walk distance was counted as 0 for the 6-minute walk tests not performed due to cardiac reasons.

Length of Stay

The mean index hospitalization stay was 8.5 days, which included an average of 3.4 days in the intensive care unit (ICU), as summarized in Table 18.

Table 18: Index Hospitalization Stay - Mitral Valve-in-Valve (Attempted Implant Population)

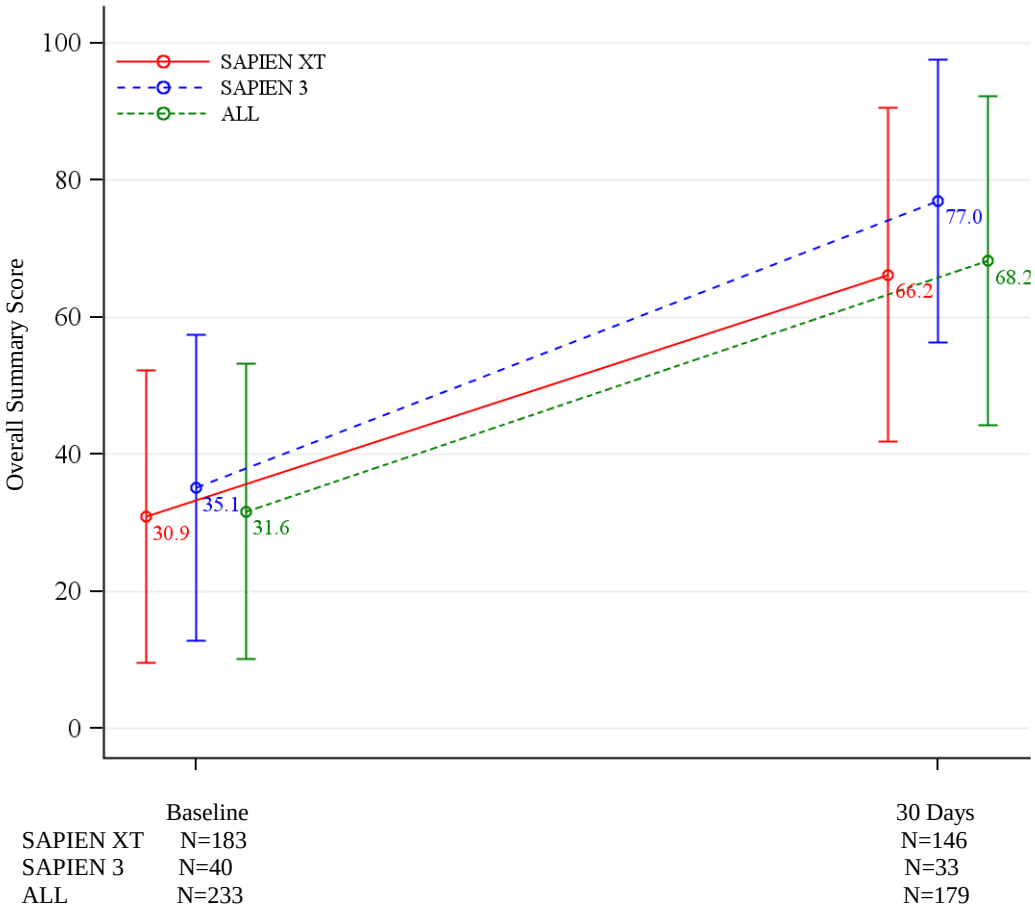
	Length (days)		
	SAPIEN XT	SAPIEN 3	All
Index hospitalization stay	8.8 ± 7.1 (241)	7.6 ± 7.4 (70)	8.5 ± 7.1 (311)
Intensive care stay	3.3 ± 4.8 (234)	3.7 ± 7.1 (63)	3.4 ± 5.3 (297)

*Mean ± SD (Total no.).

Quality of Life (QoL)

The KCCQ clinical summary scores at baseline and 30 days are shown in Figure 18. The mean KCCQ summary score improved from 31.6 at baseline to 68.2 at 30 days.

Figure 18: KCCQ Overall Summary Score - Mitral Valve-in-Valve (Valve Implant Population)



Note: Line pot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

4. Procedural Information

The procedure information is presented in Table 19. The most common delivery approach for the mitral valve-in-valve implantation was the transapical approach, which was used in 65.3% (203 of 311) of cases, followed by the transseptal approach in 27.0% (84 of 311) of cases, the transfemoral approach in 6.1% (19/311) of cases, and other alternative approaches in 1.6% (5 of 311) of cases. The procedures were considered elective in 71.0% (220/310) of cases, urgent in 27.7% (86/310) of cases, and emergent or salvage in 1.3% (4/310) of cases. Two (2) cases were aborted and 5 were converted to open heart surgery. Overall, the device was implanted successfully in 97.4% (303/311) of the cases, which was defined as correct positioning of a single prosthetic heart valve in the proper anatomical location.

Table 19: Procedural Data Summary - Mitral Valve-in-Valve (Attempted Implant Population)

Procedural Data	Summary Statistics*		
	SAPIEN XT	SAPIEN 3	All
Operator reason for procedure			
Inoperable/extreme risk	96/241 (39.8%)	11/69 (15.9%)	107/310 (34.5%)
High risk	141/241 (58.5%)	52/69 (75.4%)	193/310 (62.3%)
Intermediate risk	4/241 (1.7%)	5/69 (7.2%)	9/310 (2.9%)
Low risk	0/241 (0.0%)	1/69 (1.4%)	1/310 (0.3%)
Implant approach			
Transapical	192/241 (79.7%)	11/70 (15.7%)	203/311 (65.3%)
Transseptal	43/241 (17.8%)	41/70 (58.6%)	84/311 (27.0%)
Femoral artery	4/241 (1.7%)	15/70 (21.4%)	19/311 (6.1%)
Other	2/241 (0.8%)	3/70 (4.3%)	5/311 (1.6%)
Prior valve type			
Bioprosthetic stented	143/180 (79.4%)	35/41 (85.4%)	178/221 (80.5%)
Bioprosthetic stentless	37/180 (20.6%)	6/41 (14.6%)	43/221 (19.5%)
Procedure status			
Elective	173/241 (71.8%)	47/69 (68.1%)	220/310 (71.0%)
Urgent	64/241 (26.6%)	22/69 (31.9%)	86/310 (27.7%)
Emergency	2/241 (0.8%)	0/69 (0.0%)	2/310 (0.6%)
Salvage	2/241 (0.8%)	0/69 (0.0%)	2/310 (0.6%)
Valve size			
23 mm	22/241 (9.1%)	5/70 (7.1%)	27/311 (8.7%)
26 mm	93/241 (38.6%)	24/70 (34.3%)	117/311 (37.6%)
29 mm	126/241 (52.3%)	41/70 (58.6%)	167/311 (53.7%)
Cardiopulmonary bypass	25/241 (10.4%)	2/69 (2.9%)	27/310 (8.7%)
Status of CP Bypass			
Elective	20/25 (80.0%)	0/2 (0.0%)	20/27 (74.1%)
Emergent	5/25 (20.0%)	2/2 (100.0%)	7/27 (25.9%)
CP Bypass Time (min)	38.3 ± 51.2 (24)	148.0 ± 157.0 (2)	46.7 ± 65.4 (26)
Type of anesthesia			
General anesthesia	240/241 (99.6%)	68/69 (98.6%)	308/310 (99.4%)
Moderate sedation	0/241 (0.0%)	1/69 (1.4%)	1/310 (0.3%)
Epidural	0/241 (0.0%)	0/69 (0.0%)	0/310 (0.0%)
Combination	1/241 (0.4%)	0/69 (0.0%)	1/310 (0.3%)
Total procedure time (min)	143.6 ± 60.4 (240)	157.7 ± 107.2 (69)	146.7 ± 73.5 (309)
Fluoroscopy time (min)	23.9 ± 20.7 (223)	36.9 ± 27.3 (63)	26.8 ± 22.9 (286)
Device implanted successfully	234/241 (97.1%)	69/70 (98.6%)	303/311 (97.4%)
Procedure aborted	1/241 (0.4%)	1/70 (1.4%)	2/311 (0.6%)

Procedural Data	Summary Statistics*		
	SAPIEN XT	SAPIEN 3	All
Procedure aborted reason			
Navigation issue after successful access	1/1 (100.0%)	0/1 (0.0%)	1/2 (50.0%)
Other	0/1 (0.0%)	1/1 (100.0%)	1/2 (50.0%)
Procedure aborted action			
Conversion to open heart surgery	0/1 (0.0%)	1/1 (100.0%)	1/2 (50.0%)
Other	1/1 (100.0%)	0/1 (0.0%)	1/2 (50.0%)
Conversion to open heart surgery	4/241 (1.7%)	1/70 (1.4%)	5/311 (1.6%)
Tamponade/bleeding in the heart	4/4 (100.0%)	0/1 (0.0%)	4/5 (80.0%)
Other	0/4 (0.0%)	1/1 (100.0%)	1/5 (20.0%)
Mechanical assist device in place at start of procedure	9/241 (3.7%)	4/70 (5.7%)	13/311 (4.2%)
IABP	7/9 (77.8%)	3/4 (75.0%)	10/13 (76.9%)
Catheter-based assist device	2/9 (22.2%)	1/4 (25.0%)	3/13 (23.1%)

*Categorical measures – no./Total no. (%); continuous measures - mean ± SD (Total no.). The total no. only counted the patients with valid values at the time point.

5. Pediatric Extrapolation

In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

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

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

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The patients who underwent the aortic valve-in-valve and mitral valve-in-valve procedures overall demonstrated clinically significant improvements in valve hemodynamics from baseline to 30 days. In the aortic valve-in-valve patients, the mean aortic valve pressure gradient decreased from 39.3 ± 15.8 mmHg at baseline to 21.5 ± 11.3 mmHg at 30 days, and the percentage of patients having moderate/severe aortic

regurgitation decreased from 54.2% at baseline to 1.5% at 30 days. In the mitral valve-in-valve patients, the mean mitral valve pressure gradient decreased from 12.9 ± 5.7 mmHg at baseline to 7.1 ± 2.9 mmHg at 30 days, and the percentage of patients having moderate/severe mitral regurgitation decreased from 62.5% at baseline to 2.2% at 30 days.

The improvements in valve hemodynamics were further demonstrated with improvements in patients' functional status and QoL. In the aortic valve-in-valve patients, 85.4% of the patients had an improved NYHA class at the 30-day visit, and the mean KCCQ summary score improved from 39.4 at baseline to 75.3 at 30 days. In the mitral valve-in-valve patients, 85.6% of the patients had an improved NYHA class at the 30-day visit, and the mean KCCQ summary score improved from 31.6 at baseline to 68.2 at 30 days.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory studies and clinical data collected in the TVT Registry to support PMA approval as described above.

The Kaplan-Meier estimate of all-cause death was 4.5% and 6.8% at 30 days in the aortic and mitral valve-in-valve patients, respectively. In the aortic valve-in-valve patients, the Kaplan-Meier estimates of all stroke and aortic valve reintervention were 1.0% and 0.3%, respectively, at 30 days. In the mitral valve-in-valve patients, the Kaplan-Meier estimates of all stroke, heart failure-related readmission, and mitral valve reintervention were 0.7%, 0.8%, and 0.4%, respectively, at 30 days.

C. Benefit-Risk Conclusions

The probable benefits included improved valve hemodynamic performance, improved functional status as measured by the NYHA classification, and improved QoL at 30 days.

The probable risks of the SAPIEN 3 THV included device- and/or procedure-related complications such as death, stroke, bleeding, atrial septal defect (ASD) closure following transseptal catheterization (for mitral valve-in-valve only), cardiac arrest, atrial fibrillation, new requirement for dialysis, unplanned vascular surgery or intervention, and perforation.

Additional factors considered in determining the probable benefits and risks for the SAPIEN 3 THV included: (1) the current literature; (2) past data from IDE trials using the entire family of SAPIEN devices for a wide range of related and unrelated indications; (3) the existing experience with the approved aortic valve-in-valve indication for other transcatheter aortic valve replacement (TAVR) devices and the similarities in design between surgical aortic and mitral bioprostheses; (4) the strengths and weaknesses of available clinical data from the TVT Registry, including data quality (completeness) and quantity (number of cases); (5) observed realities in accepted clinical practice trends; (6) the severity of illness for high or inoperable surgical risk patients with failed surgical aortic or mitral bioprostheses; and (7) the unavailability of other effective treatment

options for patients at high or inoperable surgical risk for reoperative aortic and mitral valve surgery.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device. However, since transcatheter valve replacement with a SAPIEN 3 THV provides a less invasive alternative to surgical valve replacement, FDA believes many patients and their physicians would prefer the transcatheter valve replacement therapy as an alternative. For inoperable patients requiring mitral valve intervention, the patient's tolerance for risk is high because there are no good treatment alternatives. The accumulation of this substantial body of evidence based upon off-label use in the TVT Registry offers additional evidence to support this belief.

In conclusion, given the available information above, the data support that for patients with a failed (stenosed, insufficient, or combined) surgical aortic or mitral bioprosthesis who are at high or greater risk for reoperative surgical aortic or mitral valve replacement, the probable benefits of implanting an Edwards SAPIEN 3 THV outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of the safety and effectiveness of the SAPIEN 3 THV for patients with symptomatic heart disease due to a failed surgical aortic or mitral valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality $\geq$ 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

XIII. CDRH DECISION

CDRH issued an approval order on June 5, 2017. The final conditions of approval cited in the approval order are described below.

1. **SAPIEN 3 Aortic Valve-in-Valve Surveillance**: The applicant has agreed to work with the TVT Registry to ensure that FDA surveillance occurs for the SAPIEN 3 device used for the replacement of a failing surgical bioprosthetic aortic valve over the next 2 years. The applicant has also agreed to link the data to Centers for Medicare and Medicaid Services (CMS) database for long-term surveillance of these patients through 5 years post implantation. This surveillance will monitor the following: (1) device success (intra-procedure); (2) all-cause mortality, all stroke, life-threatening/major bleeding, new requirement for dialysis, 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) at 2-5 year post implantation.

2. **SAPIEN 3 Mitral Valve-in-Valve Surveillance**: The applicant has agreed to work with the TVT Registry to ensure that FDA surveillance occurs for the SAPIEN 3 device used for the replacement of a failing surgical bioprosthetic mitral valve over the next 2 years. The applicant has also agreed to link the data to CMS database for long-term surveillance of these patients through 5 years post implantation. This surveillance will monitor the following: (1) all-cause mortality, heart failure rehospitalization, and mitral valve reintervention at 30 days and 12 months; (2) 6-minute walk distance, KCCQ, and change in NYHA functional class at 30 days and 12 months; (3) device- or procedure-related adverse events, major bleeding complications, stroke and other cerebrovascular events, myocardial infarction, new requirement for dialysis, new onset atrial fibrillation, unplanned mitral valve surgery due to device/procedure failure or malfunction, requirement for valve replacement, unplanned cardiac surgery for any cause, and requirement/insertion of an implantable cardiac defibrillator at 30 days and 12 months; (4) mitral valve hemodynamics at 30 days and 12 months; (5) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 2-5 years 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).

XIV. 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.