SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Aortic valve, prosthesis, percutaneously delivered
Device Trade Name:	Edwards SAPIEN XT Transcatheter Heart Valve, model 9300TFX, 23, 26, and 29 mm, and accessories (NovaFlex+™ delivery system, models 9355FS[23,26,29] with crimp stopper and Qualcrimp crimping accessory; Ascendra+™ delivery system, models 9355AS[23,26,29]; Edwards Expandable Introducer Sheath Set, models 916ES23, 918ES26 and 920ES29; Ascendra+™ Introducer Sheath Set, models 9350IS[23,26,29]; and Edwards Crimper, model 9350CR)
Device Procode:	NPT
Applicant Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P130009/S057
Date of FDA Notice of Approval:	August 18, 2016
Priority Review:	Granted priority review status on May 31, 2016 because the availability of the device is in the best interest of the patients.

The original PMA P130009 was approved on June 16, 2014 with the indication for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 cm^2 /m^2, a mean aortic valve gradient of ≥ 40 mmHg, or a peak aortic-jet velocity of ≥ 4.0 m/s), and with native anatomy appropriate for the 23, 26, or 29 mm valve system, who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score $\geq 8\%$ or at a $\geq 15\%$ risk of mortality at 30 days). The SSED to support the original indication is available on the CDRH website http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130009b.pdf and is incorporated by reference herein. The current supplement was submitted to expand the indication for the Edwards SAPIEN XT Transcatheter Heart Valve to include patients with intermediate surgical risk for aortic valve replacement.

II. INDICATIONS FOR USE

The Edwards SAPIEN XT transcatheter heart valve (THV), model 9300TFX, and accessories are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at 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).

III. CONTRAINDICATIONS

The Edwards SAPIEN XT THV and delivery systems are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

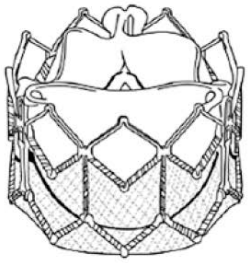
IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

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

Figure 1: SAPIEN XT Transcatheter Heart Valves

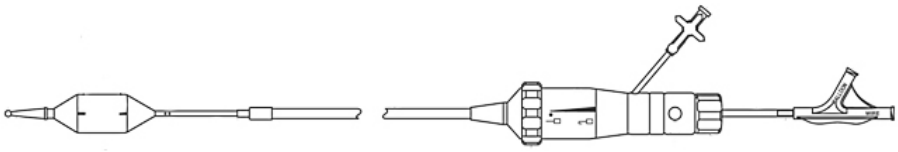


23mm and 26mm

29mm

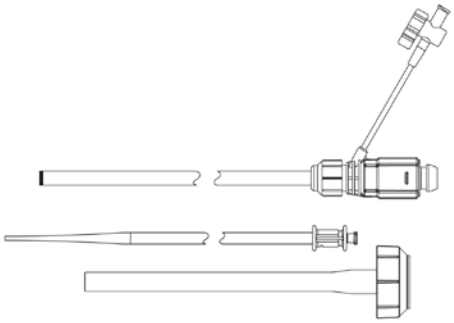
The NovaFlex+ delivery system, as shown in Figure 2, includes a handle that provides a flex wheel for articulation of the flex catheter, a tapered tip at the distal end of the delivery system to facilitate crossing the valve, a balloon catheter for deployment of the THV, and radiopaque markers.

Figure 2: NovaFlex+ Delivery System



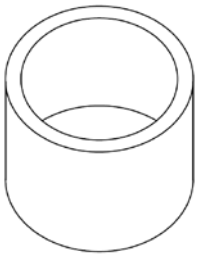
The Edwards Expandable Introducer Sheath Set, shown in Figure 3, consists of a sheath, an introducer, and a loader.

Figure 3: Edwards Expandable Introducer Sheath Set



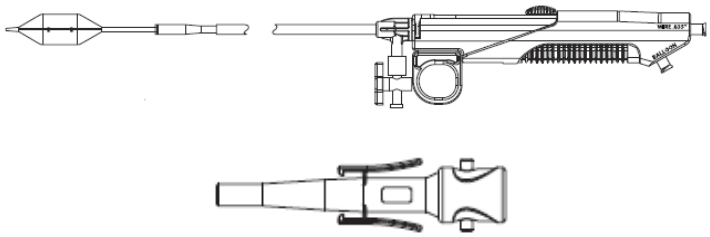
The Qualcrimp crimping accessory, as shown in Figure 4, is a non-patient contacting device that is placed around the SAPIEN XT THV to protect the leaflets during the crimping process. The Qualcrimp crimping accessory is manufactured of tubular polyester polyurethane foam that is laminated cylindrically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

Figure 4: Qualcrimp Crimping Accessory



The Ascendra+ delivery system, as shown in Figure 5, has radiopaque markers for visualization under fluoroscopy, a balloon for deployment of the THV and a handle. The system comes with a loader that is used to cover the THV during delivery. An extension tube is supplied for use with the delivery system during balloon inflation.

Figure 5: Ascendra+ Delivery System

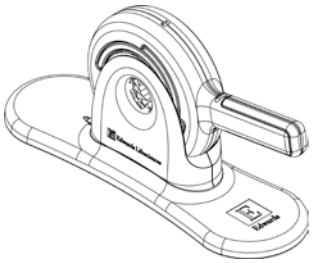


The Ascendra+ introducer sheath set, as shown in Figure 6, consists of an introducer and a sheath.

Figure 6: Ascendra+ Introducer Sheath Set

The Edwards Crimper, as shown in Figure 7, is comprised of various molded plastic components which compress the valve to a controlled aperture. The aperture is created by rotating the handle until it abuts the crimp stopper. The Edwards crimper includes a 2-piece crimp stopper (packaged with the NovaFlex+ delivery system) or a one-piece crimp stopper (packaged with the Ascendra+ delivery system).

Figure 7: Edwards Crimper



VI. ALTERNATIVE PRACTICES AND PROCEDURES

The alternative for patients with severe symptomatic native aortic valve stenosis who are deemed to be at intermediate risk for open-heart surgery is surgical aortic valve replacement (SAVR). This alternative has its own advantages and disadvantages. Patients should fully discuss this alternative with their physicians to select the method that best meets their expectations and lifestyle.

VII. MARKETING HISTORY

The SAPIEN XT THV is not marketed for the intermediate risk indication in the United States or any foreign country.

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. The potential adverse effects 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, myocardium or valvular structures that may require intervention
- Pericardial effusion or cardiac tamponade
- Embolization including air, calcific valve material or thrombus
- Infection including septicemia and endocarditis
- Heart failure
- Myocardial infarction
- Renal insufficiency or renal failure
- Conduction system defect which may require a permanent pacemaker
- Arrhythmia
- Retroperitoneal bleed
- Arteriovenous (AV) fistula or pseudoaneurysm
- Reoperation
- Ischemia or nerve injury
- Restenosis
- Pulmonary edema
- Pleural effusion
- Bleeding
- Anemia
- Abnormal lab values (including electrolyte imbalance)
- Hypertension or hypotension
- Allergic reaction to anesthesia, contrast media, or device materials
- Hematoma
- Syncope
- Pain or changes at the access site
- Exercise intolerance or weakness

- Inflammation
- Angina
- Heart murmur
- Fever

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

- Cardiac arrest
- Cardiogenic shock
- Emergency cardiac surgery
- Cardiac failure or low cardiac output
- Coronary flow obstruction/transvalvular flow disturbance
- Device thrombosis requiring intervention
- Valve thrombosis
- Device embolization
- Device migration or malposition requiring intervention
- Valve deployment in unintended location
- Valve stenosis
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, or stenosis)
- Device degeneration
- Paravalvular or transvalvular leak
- Valve regurgitation
- Hemolysis
- Device explants
- Nonstructural dysfunction
- Mechanical failure of delivery system, and/or accessories
- Non-emergent reoperation

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

IX. SUMMARY OF PRECLINICAL STUDIES

No additional preclinical testing was necessary for the current supplement. A summary of previously reported preclinical studies can be found in the SSED for the original PMA (http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130009b.pdf).

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study in the U.S. and Canada to establish a reasonable assurance of safety and effectiveness of transcatheter aortic valve replacement (TAVR) with the Edwards SAPIEN XT THV in patients with severe native calcific aortic stenosis who were at intermediate risk for surgery under IDE G090216 (entitled the "PARTNER

II" trial). Data from the PARTNER II Trial Intermediate Risk Cohort A (denoted as "PIIA") was the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

PIIA was a 1:1 randomized, controlled study independently powered to compare the results of TAVR with the SAPIEN XT to traditional, open-heart aortic valve surgery (i.e., surgical aortic valve replacement or SAVR). The SAPIEN XT THV was available in sizes 23 mm, 26 mm, and 29 mm.

Patients were treated from December 2011 to November 2013. The database reflected data collected through February 1, 2016 and included 1,011 patients in the SAPIEN XT arm and 1,021 patients in the SAVR arm at 57 investigational sites in the U.S. and Canada.

The study used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify the applicant of any safety or compliance issues and a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint-related events reported during the trial. The CEC adjudicated the events per pre-established definitions, which were primarily Valve Academic Research Consortium-1 (VARC-1)[1] definitions with the following exceptions:

- Acute kidney injury (AKI) was adjudicated with a modified VARC-1 definition in which the CEC identified the peak creatinine within 30 days of the index procedure, 30 days to 1 year, and 1 year to 2 years to determine if it met the definition of AKI.
- Aortic valve reintervention, hemolysis, and pericarditis were adjudicated per study protocol definition.
- Rehospitalization for symptoms of aortic stenosis and/or complications of the valve procedure was adjudicated using the study protocol and VARC-1 as guidelines.
- Bleeding events were adjudicated irrespective of whether there was an identifiable, overt source of bleeding and could be adjudicated based on transfusion or hemoglobin drop alone.

Also, an electrocardiogram (ECG) core laboratory was used for independent analysis of rhythm, and an echocardiographic core laboratory for all echocardiograms.

1. Clinical Inclusion and Exclusion Criteria

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

– Patient had senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient > 40 mmHg or jet velocity greater than 4.0 m/s

and an initial aortic valve area (AVA) of $\leq$ 0.8 cm^2 or indexed effective orifice area (EOA) < 0.5 cm^2/m^2. Qualifying echo must be within 45 days of the date of the procedure.

- Patient was symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater.
- The Heart Team agreed (and verified in the case review process) that valve implantation would likely benefit the patient.
- The study patient or his/her legal representative had been informed of the nature of the study, agreed to its provisions and provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.
- The study patient agreed to comply with all required post-procedure follow-up visits including annual visits through 5 years and analysis close date visits, which were conducted as a phone follow-up.

Once eligibility in accordance to the above criteria was established, patients were assessed for operability. Patients who were candidates for SAVR needed to meet the following additional inclusion criteria:

- STS $\geq$ 4.
- Heart Team (including examining cardiac surgeon) agreed on eligibility including assessment that TAVR or SAVR was appropriate.
- Heart Team agreed (*a priori*) on treatment strategy for concomitant coronary disease (if present).
- Study patient agreed to undergo SAVR if randomized to the control arm.

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

- Heart Team assessment of inoperability (including examining cardiac surgeon).
- Evidence of an acute myocardial infarction (MI) $\leq$ 1 month (30 days) before the intended treatment (defined as: Q wave MI, or non-Q wave MI with total creatine kinase (CK) elevation of CK-MB $\geq$ twice normal in the presence of MB elevation and/or troponin level elevation [WHO definition]).
- Aortic valve was a congenital unicuspid or congenital bicuspid valve, or was non-calcified.
- Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
- Preexisting mechanical or bioprosthetic valve in any position.
- Complex coronary artery disease:
    - Unprotected left main coronary artery
    - SYNTAX score > 32 (in the absence of prior revascularization)
- Any therapeutic invasive cardiac procedure resulting in a permanent implant that was performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease). Implantation of a permanent pacemaker was not excluded.

- Any patient with a balloon aortic valvuloplasty (BAV) within 30 days of the procedure (unless BAV was a bridge to procedure after a qualifying echo).
- Patients with planned concomitant surgical or transcatheter ablation for atrial fibrillation.
- Leukopenia (WBC < 3,000 cells/mL), acute anemia (Hgb < 9 g/dL), or thrombocytopenia (Plt < 50,000 cells/mL).
- Hypertrophic cardiomyopathy with or without obstruction.
- Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20%.
- Echocardiographic evidence of intracardiac mass, thrombus, or vegetation.
- Active upper gastrointestinal (GI) bleeding within 3 months (90 days) prior to procedure.
- A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.
- Native aortic annulus size < 18 mm or > 27 mm as measured by echocardiogram.
- Clinically (by neurologist) or neuroimaging confirmed stroke or transient ischemic attack (TIA) within 6 months (180 days) of the procedure.
- Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at the time of screening.
- Estimated life expectancy < 24 months (730 days) due to carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease.
- Expectation that patient would not improve despite treatment of aortic stenosis
- Current participation in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but had since become commercially available, were not considered investigational trials.
- It was known that the patient was currently enrolled in the PARTNER I Trial or was withdrawn from the PARTNER I Trial prior to endpoint analysis.
- Active bacterial endocarditis within 6 months (180 days) of procedure.
- Patient refuses aortic valve replacement surgery.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at discharge, 30 days, 6 months, 12 months, and 24 months, and will continue thereafter to a minimum of 10 years post procedure. Preoperative and post-operative assessments included physical assessment and patient interview, laboratory measurements, imaging tests, and quality of life (QoL) questionnaire. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

The primary endpoint was a non-hierarchical composite of all-cause death or disabling (major) stroke at 2 years (730 days). The analysis was a non-inferiority comparison. Events occurring on day 730 or earlier were included in the evaluation; those occurring after day 730 were not included. The primary hypothesis was as

follows:

H_0: $r_T / r_C \geq 1 + \Delta$
H_A: $r_T / r_C < 1 + \Delta$

where r_T and r_C denote the true event proportions in the test and control arms, respectively, and Δ denotes the non-inferiority margin. The value of Δ was chosen to be 0.20. The test was performed as a one-sided test at $\alpha = 0.025$. The event proportions r_T and r_C were computed using the Kaplan-Meier (K-M) algorithm. The standard errors of the K-M estimators were computed using Greenwood's formula.

There were six (6) pre-specified key secondary endpoints for labeling:

1) Days alive and out of hospital (DAOH) to 2 years
2) NYHA classification at the 2-year visit
3) 6-minute walk test (6MWT) at the 2-year visit
4) Effective orifice area (EOA) at the 2-year visit
5) Total aortic regurgitation (AR) at the 2-year visit
6) 6MWT improvement from baseline to 2 years (for SAPIEN XT arm only)

These six (6) secondary endpoints were all assessed as a non-inferiority comparison of SAPIEN XT to SAVR with the exception of 6MWT improvement from baseline to 2 years, which was a superiority comparison. The family-wise Type I error rate was controlled at $\alpha = 0.05$ via the Hochberg method.

The hypothesis for DAOH at 2 years was as follows:

H_0: $DAOH_{TEST} - DAOH_{CONTROL} \leq -35$ days
H_A: $DAOH_{TEST} - DAOH_{CONTROL} > -35$ days

The hypothesis for NYHA classification at 2 years was as follows:

H_0: $NYHA_{TEST} - NYHA_{CONTROL} \geq 0.25$
H_A: $NYHA_{TEST} - NYHA_{CONTROL} < 0.25$

The hypothesis for 6MWT at 2 years was as follows:

H_0: $6MWT_{TEST} - 6MWT_{CONTROL} \leq -70$ meters
H_A: $6MWT_{TEST} - 6MWT_{CONTROL} > -70$ meters

The hypothesis for EOA at 2 years was as follows:

H_0: $EOA_{TEST} - EOA_{CONTROL} \leq -0.2$ cm^2
H_A: $EOA_{TEST} - EOA_{CONTROL} > -0.2$ cm^2

The hypothesis for total AR at 2 years was as follows:

H_0: $AR_{TEST} - AR_{CONTROL} \geq 0.25$
H_A: $AR_{TEST} - AR_{CONTROL} < 0.25$

The hypothesis for 6MWT improvement from baseline to 2 years was as follows:

H_0: $6MWT_{BASELINE} = 6MWT_{2\text{-}YEARS}$
H_A: $6MWT_{BASELINE} \neq 6MWT_{2\text{-}YEARS}$

There were three (3) additional adjunctive secondary endpoints as follows:

1) Non-hierarchical composite of the following events evaluated at two time points: (i) 30 days or hospital discharge, whichever is longer; and (ii) 31 days to 2 years:
    - All stroke and transient ischemic attack (TIA)
    - Myocardial infarction (MI)
    - Vascular complications (VARC-1)
    - Life-threatening bleeding (VARC-1)
    - Reoperation or catheter-based intervention for valve thrombosis, valve displacement, or other valve- or procedure-related complication
    - Pericarditis
    - Hemolysis
    - Mediastinitis
    - Endocarditis
    - Aortic insufficiency (VARC-1)
    - Aortic stenosis (VARC-1)
    - Permanent pacemaker insertion
    - Mitral valve injury or insufficiency
    - Renal insufficiency
2) Non-hierarchical composite of all stroke, major vascular complications, or aortic valve reintervention at 2 years
3) Non-hierarchical composite of all-cause death, disabling (major) stroke, or rehospitalization at 2 years

B. Accountability of the PMA Cohort

At the time of database lock, of the 2032 patients enrolled in the PMA study, 73.5% (1494) patients are available for analysis at the completion of the study, the 2-year post-operative visit. Table 1 presents patient accountability in the PIIA trial. The SAPIEN XT patients had either a transfemoral (TF) or non-transfemoral (non-TF) access.

Table 1: Patient Accountability

	Intent to Treat Population*	As Treated Population†	Valve Implant Population‡
SAPIEN XT	1011	994	974
TF	775	762	749
Non-TF	236	232	225
SAVR	1021	944	936

*Intent to Treat (ITT) population: All randomized patients.

†As Treated (AT) population: All enrolled/randomized patients for whom the index procedure was started. Patients were analyzed according to the valve used in the initial implant attempt.

‡Valve Implant (VI) population: All AT patients whose valve implant process was completed.

In the SAPIEN XT intent-to-treat (ITT) population, 187 patients exited the study prior to the 2-year visit. Of the remaining 824 patients who were due for the 2-year visit, 784 patients (95.1%) completed the 2-year visit, and 40 patients (4.9%) missed the 2-year visit.

In the SAVR ITT population, 216 patients exited the study prior to the 2-year visit. Of the remaining 805 patients who were due for the 2-year visit, 710 patients (88.2%) completed the 2-year visit, and 95 patients (11.8%) missed the 2-year visit.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an aortic stenosis valve replacement study performed in the US. The demographics and baseline characteristics of the ITT population are presented in Table 2. Among the SAPIEN XT population, 775 patients were implanted via the TF access route and 236 patients via the non-TF access route, including transapical (TA) or transaortic (TAo) access.

Table 2: Demographics and Baseline Characteristics (ITT Population)

Demographics & Characteristic*	SAPIEN XT			SAVR (N = 1021)
	All (N = 1011)	TF only (N = 775)	Non-TF Only (N = 236)	
Age (years)	81.5±6.7	81.8±6.7	80.6±6.6	81.7±6.7
Male Sex	548/1011 (54.2%)	426/775 (55.0%)	122/236 (51.7%)	560/1021 (54.8%)
Society of Thoracic Surgeons (STS) score	5.8±2.1	5.8±2.1	6.0±2.1	5.8±1.9
New York Heart Association (NYHA) class				
I/II	229/1011 (22.7%)	174/775 (22.5%)	55/236 (23.3%)	244/1020 (23.9%)

Demographics & Characteristic*	SAPIEN XT			SAVR (N = 1021)
	All (N = 1011)	TF only (N = 775)	Non-TF Only (N = 236)	
III/IV	782/1011 (77.3%)	601/775 (77.5%)	181/236 (76.7%)	776/1020 (76.1%)
Coronary Artery Disease	700/1011 (69.2%)	531/775 (68.5%)	169/236 (71.6%)	679/1021 (66.5%)
Previous Myocardial Infarction	185/1011 (18.3%)	137/775 (17.7%)	48/236 (20.3%)	179/1021 (17.5%)
Previous Reintervention				
Coronary Artery Bypass Grafting	239/1011 (23.6%)	179/775 (23.1%)	60/236 (25.4%)	261/1021 (25.6%)
Percutaneous coronary intervention	274/1011 (27.1%)	202/775 (26.1%)	72/236 (30.5%)	282/1021 (27.6%)
Prior aortic valvuloplasty	51/1011 (5.0%)	35/775 (4.5%)	16/236 (6.8%)	50/1021 (4.9%)
Cerebral vascular accident	103/1011 (10.2%)	67/775 (8.6%)	36/236 (15.3%)	104/1021 (10.2%)
Peripheral vascular disease	282/1011 (27.9%)	167/775 (21.5%)	115/236 (48.7%)	336/1021 (32.9%)
Chronic obstructive pulmonary disease				
Any	321/1011 (31.8%)	228/775 (29.4%)	93/236 (39.4%)	306/1021 (30.0%)
Oxygen-dependent	34/1011 (3.4%)	20/775 (2.6%)	14/236 (5.9%)	32/1021 (3.1%)
Atrial fibrillation	313/1011 (31.0%)	245/775 (31.6%)	68/236 (28.8%)	359/1021 (35.2%)
Permanent pacemaker	118/1011 (11.7%)	91/775 (11.7%)	27/236 (11.4%)	123/1021 (12.0%)
Pulmonary hypertension	29/1011 (2.9%)	25/775 (3.2%)	4/236 (1.7%)	25/1019 (2.5%)
Frailty	12/1011 (1.2%)	11/775 (1.4%)	1/236 (0.4%)	15/1019 (1.5%)
Porcelain aorta	0/1011 (0.0%)	0/775 (0.0%)	0/236 (0.0%)	1/1019 (0.1%)
Chest deformities that preclude an open chest procedure	0/1011 (0.0%)	0/775 (0.0%)	0/236 (0.0%)	0/1019 (0.0%)
Cirrhosis	0/1011 (0.0%)	0/775 (0.0%)	0/236 (0.0%)	5/1019 (0.5%)
Echocardiographic findings (VI Population)				

Demographics & Characteristic*	SAPIEN XT			SAVR (N = 1021)
	All (N = 1011)	TF only (N = 775)	Non-TF Only (N = 236)	
Effective orifice area (EOA) - cm^2	0.7±0.2	0.7±0.2	0.7±0.2	0.7±0.2
Mean aortic valve gradient - mmHg	45.0±13.3	45.0±13.6	44.7±12.3	44.7±12.6
Moderate or severe mitral regurgitation	146/875 (16.7%)	116/677 (17.1%)	30/198 (15.2%)	153/841 (18.2%)

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

D. Safety and Effectiveness Results

1. Primary Endpoint

The results of the composite primary endpoint of all-cause death or disabling (major) stroke at 2 years and each component are presented for the ITT population in Table 3 and Figures 8-10. The K-M estimate of the composite event for SAPIEN XT was found to be non-inferior to that for SAVR (19.3% vs. 21.1%; *p*=0.0014).

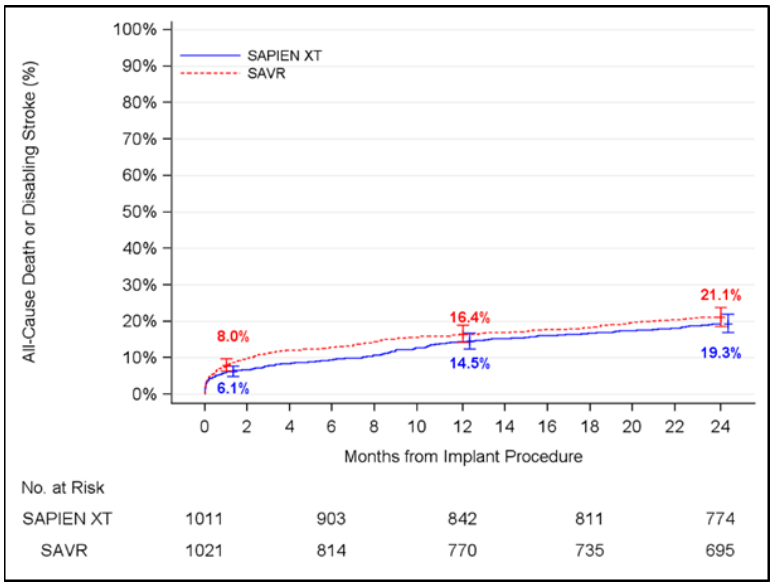
Table 3: All-Cause Death or Disabling (Major) Stroke at 2 Years (ITT Population)

Event	SAPIEN XT (N = 1011)					SAVR (N = 1021)				
	No. of Events*	Patients with Event	No. Patients at Risk	K-M Estimate†		No. of Events*	Patients with Event	No. Patients at Risk	K-M Estimate†	
				Point Estimate	Standard Error				Point Estimate	Standard Error
All-cause death or disabling stroke at 2 years	229	192	774	19.3%	1.3%	235	202	695	21.1%	1.3%
All-cause death at 2 years	166	166	798	16.7%	1.2%	170	170	719	18.0%	1.3%
Disabling stroke at 2 years	63	59	774	6.2%	0.8%	65	61	695	6.4%	0.8%

*Events with missing or incomplete onset dates are excluded from the analysis.

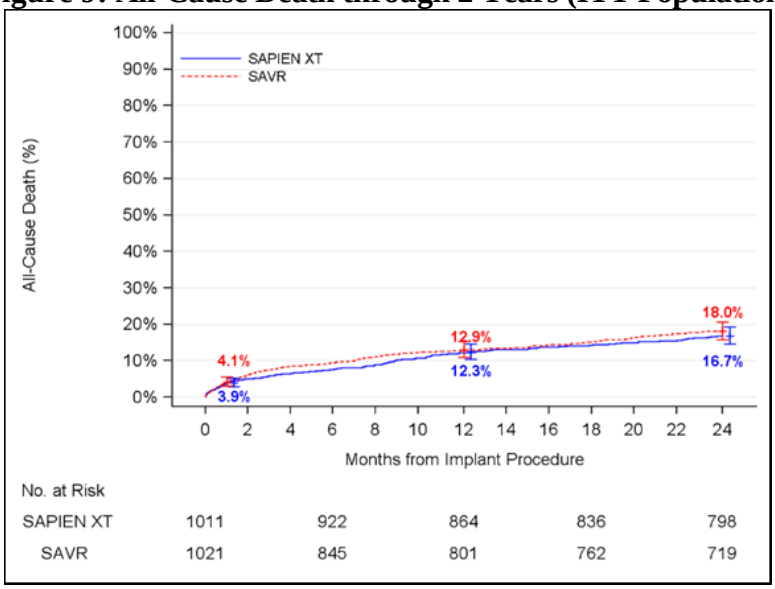
†K-M estimates are provided at 2 years (day 730) and use the first event per patient. Events occurring after 730 days are not included in the analysis.

Figure 8: All-Cause Death or Disabling (Major) Stroke through 2 Years (ITT Population)



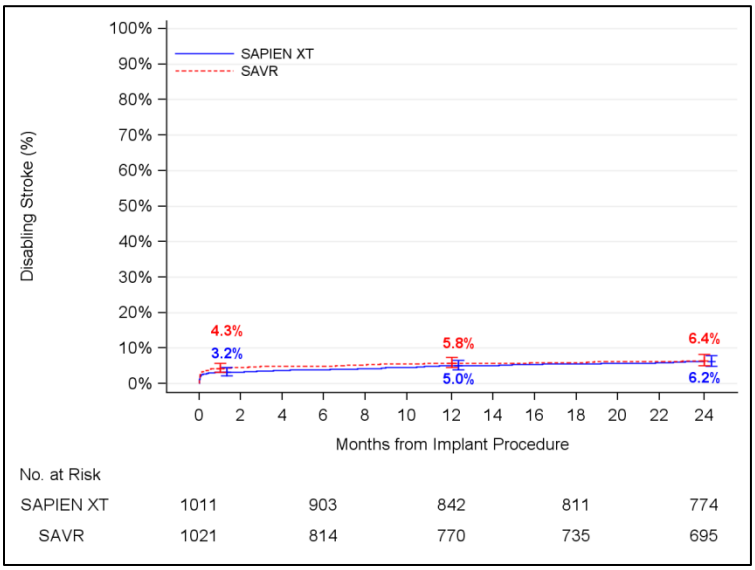
Note: The confidence intervals at 30 days and 12 months were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Figure 9: All-Cause Death through 2 Years (ITT Population)



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

Figure 10: Disabling (Major) Stroke through 2 Years (ITT Population)



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

The results for the primary endpoint and its components for the SAPIEN XT ITT population by access approach are presented in Table 4. The TF access had clinically lower all-cause death and disabling (major) stroke rates than did the non-TF access.

Table 4: All-Cause Death or Disabling (Major) Stroke to 2 Years by Access Approach (SAPIEN XT ITT Population)

	TF (N = 775)					Non-TF (N = 236)				
Event	No. of Events*	Patients with Event	No. Patients at Risk	K-M Estimate†		No. of Events*	Patients with Event	No. Patients at Risk	K-M Estimate†	
				Point Estimate	Standard Error				Point Estimate	Standard Error
All-cause death or disabling stroke at 2 years	151	128	612	16.8%	1.4%	78	64	162	27.7%	3.0%
All-cause death at 2 year	108	108	630	14.2%	1.3%	58	58	168	25.2%	2.9%

Event	TF (N = 775)					Non-TF (N = 236)				
	No. of Events*	Patients with Event	No. Patients at Risk	K-M Estimate†		No. of Events*	Patients with Event	No. Patients at Risk	K-M Estimate†	
				Point Estimate	Standard Error				Point Estimate	Standard Error
All-cause death or disabling stroke at 2 years	151	128	612	16.8%	1.4%	78	64	162	27.7%	3.0%
Disabling stroke at 2 years	43	39	612	5.3%	0.8%	20	20	162	9.1%	1.9%

*Events with missing or incomplete onset dates are excluded from the analysis.
†Kaplan-Meier estimates are provided at 2 years (day 730) and use the first event per patient. Events occurring after 730 days are not included in the analysis.

2. Key Secondary Endpoints

The results for the six (6) key secondary endpoints using the Hochberg's step-up method for multiple tests are presented for the ITT population in Table 5 and for the as- treated (AT) population in Table 6. SAPIEN XT was found to be non-inferior to SAVR in NYHA class at 2 years, DAOH to 2 years, 6MWT distance at 2 years, and EOA at 2 years. The 6MWT distance at 2 years was superior to that at baseline in the SAPIEN XT patients. However, the result failed to reject the null hypothesis that the mean total AR in the SAPIEN XT arm was worse than that in the SAVR arm by a margin of 0.25.

Table 5: Key Secondary Endpoints Comparisons Using the Hochberg Method (ITT/VI Population)

Endpoint	Summary Statistics*		Difference†	p-value	Reference α	Statistical Inference
	SAPIEN XT	SAVR				
Total AR at 2 years‡ (VI)	1.2±1.0 (606)	0.5±0.7 (520)	0.8 (0.67, 0.86)	>0.9999	0.05	Fail to reject null hypothesis and move on to next line

Endpoint	Summary Statistics*		Difference†	p-value	Reference α	Statistical Inference
	SAPIEN XT	SAVR				
Change in 6MWT distance from baseline to 2 years (SAPIEN XT only; ITT)	14.5±128.7 (604)	NA	NA	0.0057	0.025	Reject null hypothesis and conclude non-inferiority for the rest of endpoints
NYHA class at 2 years (ITT)	1.5±0.7 (737)	1.4±0.6 (649)	0.1 (0.0, 0.2)	<0.0001		
DAOH to 2 years (ITT)	637.5±203.2 (960)	619.0±223.1 (885)	18.6 (-1.0, 38.1)	<0.0001		
6MWT distance at 2 years (ITT)	203.2±132.4 (615)	209.8±153.5 (513)	-6.6 (-23.5, 10.3)	<0.0001		
EOA at 2 years (VI)	1.5±0.4 (567)	1.4±0.4 (488)	0.1 (0.09, 0.19)	<0.0001		

*Mean ± SD (n)
†Difference (95% CI)
‡Total AR was graded as: none=0, trace=1, mild and mild-moderate=2, moderate and moderate-severe=3, and severe=4. It was treated as a continuous variable and compared using the t-test.

Table 6: Key Secondary Endpoints Comparisons Using the Hochberg Method (AT/VI Population)

Endpoint	Summary Statistics*		Difference†	p-value	Reference α	Statistical Inference
	SAPIEN XT	SAVR				
Total AR at 2 years‡ (VI)	1.2±1.0 (606)	0.5±0.7 (520)	0.8 (0.7, 0.9)	>0.9999	0.05	Fail to reject null hypothesis and move on to next line
Change in 6MWT distance from baseline to 2 years (SAPIEN XT only; AT)	14.5±128.7 (604)	NA	NA	0.0057	0.025	Reject null hypothesis and conclude non-inferiority for the rest of endpoints

Endpoint	Summary Statistics*		Difference†	p-value	Reference α	Statistical Inference
	SAPIEN XT	SAVR				
NYHA at the 2-year visit (AT)	1.5±0.7 (737)	1.4±0.6 (649)	0.1 (0.0, 0.2)	<0.0001		
DAOH to 2 years (AT)	638.8±201.5 (958)	619.5±222.4 (883)	19.2 (-0.2, 38.7)	<0.0001		
6MWT distance at the 2-year visit (AT)	203.2±132.4 (615)	209.8±153.5 (513)	-6.6 (-23.5, 10.3)	<0.0001		
EOA at 2 years (VI)	1.5±0.4 (567)	1.4±0.4 (488)	0.14 (0.09, 0.20)	<0.0001		

*Mean ± SD (n)
†Difference (95% CI)
‡Total AR was graded as: none=0, trace=1, mild and mild-moderate=2, moderate and moderate-severe=3, and severe=4. It was treated as a continuous variable and compared using the t-test.

3. Adjunctive Secondary Endpoints

The results for the first adjunctive secondary composite endpoint of 14 pre-specified site-reported events are presented in Tables 7 and 8.

Table 7: Composite Endpoint of 14 Pre-specified Site-Reported Events to 30 Days or Discharge (AT Population)

Adverse Event	SAPIEN XT (N = 994)		SAVR (N = 944)		Relative Risk SAPIEN XT versus SAVR
	Events*	Patients with Event	Events*	Patients with Event	
Composite event to 30 days or discharge†	573	378/994 (38.0%)	714	493/944 (52.2%)	0.73

*Imputed dates are used for events with incomplete onset dates.
†The composite event consists of all stroke and TIA; myocardial infarction; vascular complications; life-threatening bleeding; reoperation for catheter-based intervention for valve thrombosis, valve displacement, or other valve- or procedure-related complication; pericarditis; hemolysis; mediastinitis; endocarditis; aortic insufficiency; aortic stenosis; permanent pacemaker implantation; mitral valve injury or insufficiency; or renal insufficiency.

Table 8: Composite Endpoint of 14 Pre-specified Site-Reported Events from Day 31 to 2 Years (AT Population)

Adverse Event	SAPIEN XT (N = 994)		SAVR (N = 944)		Relative Risk SAPIEN XT versus SAVR
	Events/Patients with Event/No. at Risk*	K-M Estimate (Standard Error)	Events/Patients with Event/No. at Risk*	K-M Estimate (Standard Error)	
Composite event from day 31 to 2 years†	428/284/594	31.0% (1.53%)	344/225/568	26.5% (1.52%)	1.17

*Events with missing or incomplete onset dates and those occurring before day 31 or after day 730 are excluded from the analysis.

†The composite event consists of all stroke and TIA; myocardial infarction; vascular complications; life-threatening bleeding; reoperation for catheter-based intervention for valve thrombosis, valve displacement, or other valve- or procedure-related complication; pericarditis; hemolysis; mediastinitis; endocarditis; aortic insufficiency; aortic stenosis; permanent pacemaker implantation; mitral valve injury or insufficiency; or renal insufficiency.

The result for the second adjunctive secondary composite endpoint of CEC-adjudicated all stroke, major vascular complications, or aortic valve reinterventions at 2 years is presented in Table 9 for the AT population.

Table 9: All Stroke, Major Vascular Complications, or Aortic Valve Reintervention to 2 Years (AT Population)

Event	SAPIEN XT (N = 994)		SAVR (N = 944)		Relative Risk SAPIEN XT vs SAVR
	Events/Patients with Event/No. at Risk*	K-M Estimate (Standard Error)	Events/Patients with Event/No. at Risk*	K-M Estimate (Standard Error)	
All stroke, major vascular complications, or reinterventions at 2 years	210/176/684	18.1% (1.24%)	156/132/644	14.4% (1.16%)	1.26

*Events with missing or incomplete onset dates and those occurring before day 31 or after day 730 are excluded from the analysis.

The result for the third adjunctive secondary composite endpoint of All-cause mortality, disabling stroke, or rehospitalization at 2 years is presented in Table 10 for the AT population.

Table 10: All-Cause Death, Disabling (Major) Stroke, or Rehospitalization to 2 Years (AT Population)

Event	SAPIEN XT (N = 994)		SAVR (N = 944)		Relative Risk SAPIEN XT vs SAVR
	Events/Patients with Event/No. at Risk*	K-M Estimate (Standard Error)	Events/Patients with Event/No. at Risk*	K-M Estimate (Standard Error)	
All-cause death, disabling stroke, or rehospitalization at 2 years	486/313/655	31.7% (1.48%)	428/298/600	32.0% (1.53%)	0.99

*Events with missing or incomplete onset dates and those occurring before day 31 or after day 730 are excluded from the analysis.

4. Adverse Events

Results for some key CEC-adjudicated adverse events through 2 years are presented in Table 11 for the ITT population.

Table 11: Key CEC-Adjudicated Adverse Events (ITT Population)

Event*	SAPIEN XT			SAVR (N = 1021)
	Overall (N = 1011)	TF Access (N = 775)	Non-TF Access (N = 236)	
30 Days				
Acute kidney injury	192 (19.0)	106 (13.7)	86 (36.4)	327 (32.0)
Stage III	13 (1.3)	4 (0.5)	9 (3.8)	31 (3.0)
Death	39 (3.9)	23 (3.0)	16 (6.8)	41 (4.0)
Cardiac death	33 (3.3)	21 (2.7)	12 (5.1)	32 (3.1)
Non-cardiac death	6 (0.6)	2 (0.3)	4 (1.7)	9 (0.9)
Stroke	55 (5.4)	32 (4.1)	23 (9.7)	61 (6.0)
Disabling stroke	32 (3.2)	18 (2.3)	14 (5.9)	43 (4.2)
Non-disabling stroke	23 (2.3)	14 (1.8)	9 (3.8)	18 (1.8)
Myocardial infarction	12 (1.2)	5 (0.6)	7 (3.0)	19 (1.9)
Major vascular complication	80 (7.9)	66 (8.5)	14 (5.9)	51 (5.0)
Life threatening/disabling bleeding	105 (10.4)	52 (6.7)	53 (22.5)	442 (43.3)
Aortic valve reintervention	4 (0.4)	3 (0.4)	1 (0.4)	0 (0.0)
Endocarditis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhythm disturbance	85 (8.4)	62 (8.0)	23 (9.7)	68 (6.7)

Event*	SAPIEN XT			SAVR (N = 1021)
	Overall (N = 1011)	TF Access (N = 775)	Non-TF Access (N = 236)	
requiring permanent pacemaker				
2 Years				
Acute kidney injury	326 (32.2)	206 (26.6)	120 (50.8)	404 (39.6)
Stage III	36 (3.6)	18 (2.3)	18 (7.6)	57 (5.6)
Death	166 (16.4)	108 (13.9)	58 (24.6)	170 (16.7)
Cardiac death	97 (9.6)	67 (8.6)	30 (12.7)	105 (10.3)
Non-cardiac death	69 (6.8)	41 (5.3)	28 (11.9)	65 (6.4)
Stroke	91 (9.0)	62 (8.0)	29 (12.3)	85 (8.3)
Disabling stroke	59 (5.8)	39 (5.0)	20 (8.5)	61 (6.0)
Non-disabling stroke	33 (3.3)	24 (3.1)	9 (3.8)	27 (2.6)
Myocardial infarction	33 (3.3)	21 (2.7)	12 (5.1)	37 (3.6)
Major vascular complication	86 (8.5)	69 (8.9)	17 (7.2)	55 (5.4)
Life threatening/disabling bleeding	169 (16.7)	101 (13.0)	68 (28.8)	471 (46.1)
Aortic valve reintervention	13 (1.3)	9 (1.2)	4 (1.7)	5 (0.5)
Endocarditis	11 (1.1)	10 (1.3)	1 (0.4)	6 (0.6)
Rhythm disturbance requiring permanent pacemaker	114 (11.3)	85 (11.0)	29 (12.3)	96 (9.4)

*Categorical measures - n/Total no. (%); Events with missing or incomplete onset dates are excluded from the analysis.

5. Other Results

Procedural Information

Overall, in the SAPIEN XT AT population the mean duration in the catheterization laboratory was 209.0±59.5 min, the mean total procedure time was 102.7±51.4 min, and the mean total anesthesia time was 207.1±64.7 min. These duration times were slightly shorter in the TF group. General anesthesia was used in the vast majority of cases; 7.8% of the TF patients had conscious sedation. Correct positioning of the valve was achieved in 98.5% of the patients. Nineteen (19) patients (1.7% of TF patients and 2.6% of non-TF patients) were implanted with a second valve. Two (2) patients (0.5%) experienced valve dislodgement. Three (3) patients (0.3%) experienced annular rupture.

In the SAVR AT population, the mean duration in the operating room was 332.3±96.9 min, the mean total procedure time was 236.8±86.9 min, and the mean anesthesia time was 333.0±108.6 min. General anesthesia was used in all patients. It was difficult to wean 26 patients (2.8%) from cardiopulmonary bypass, which was terminated in the majority of cases with intra-aortic balloon pump and/or inotropes.

Valve Performance

The measurements of EOA, mean gradient, peak gradient, total aortic regurgitation (AR), and aortic paravalvular leak (PVL) are presented in Figures 11-15. The increase in EOA and decrease in gradient were sustained at 2 years. In the SAPIEN XT arm, the proportion of patients with total AR ≥ moderate was 11.0% at baseline, 3.8% at 30 days, 4.0% at 1 year, and 9.4% at 2 years, while in the SAVR arm, the proportion of patients with total AR ≥ moderate was 12.0% at baseline, 0.7% at 30 days, 0.3% at 1 year, and 0.8% at 2 years. The proportion of patients with aortic PVL ≥ moderate was 3.8% at 30 days, 3.4% at 1 year, and 8.0% at 2 years in the SAPIEN XT arm, as compared to 0.5% at 30 days, 0.3% at 1 year, and 0.6% at 2 years in the SAVR arm.

Figure 11: Effective Orifice Area (VI Population)

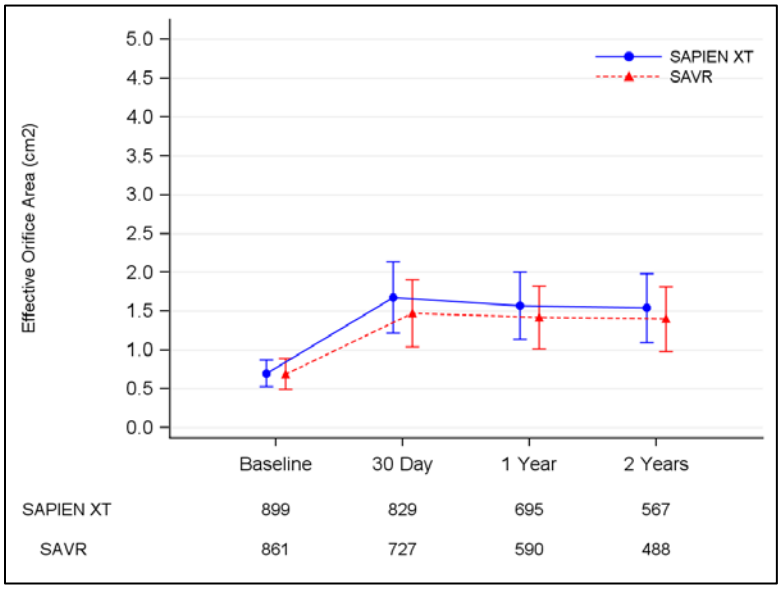


Figure 12: Mean Gradient (VI Population)

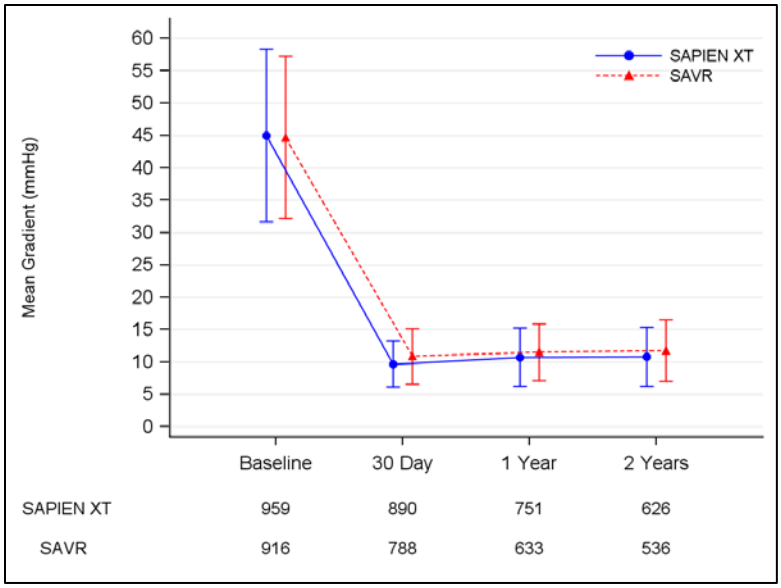


Figure 13: Peak Gradient (VI Population)

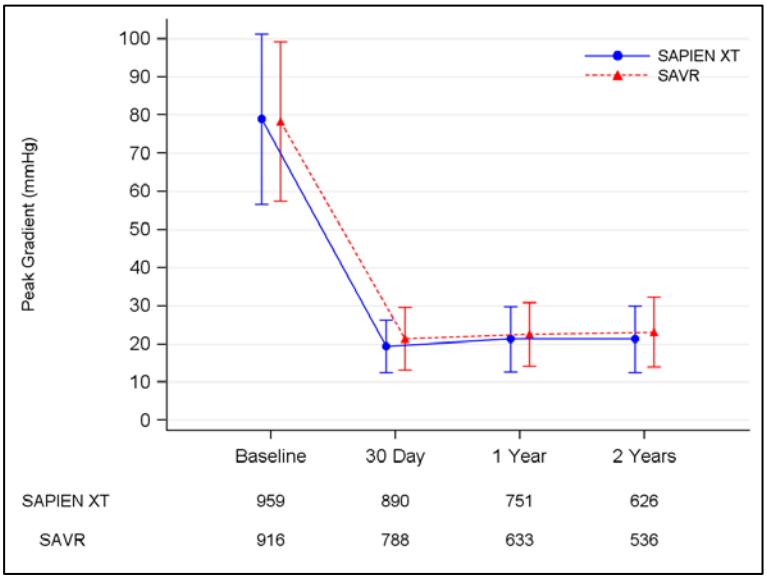


Figure 14: Total Aortic Regurgitation (VI Population)

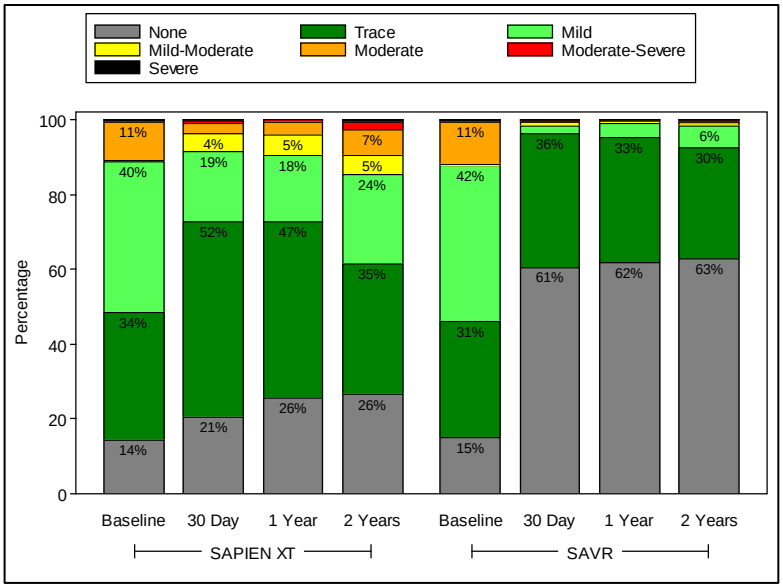
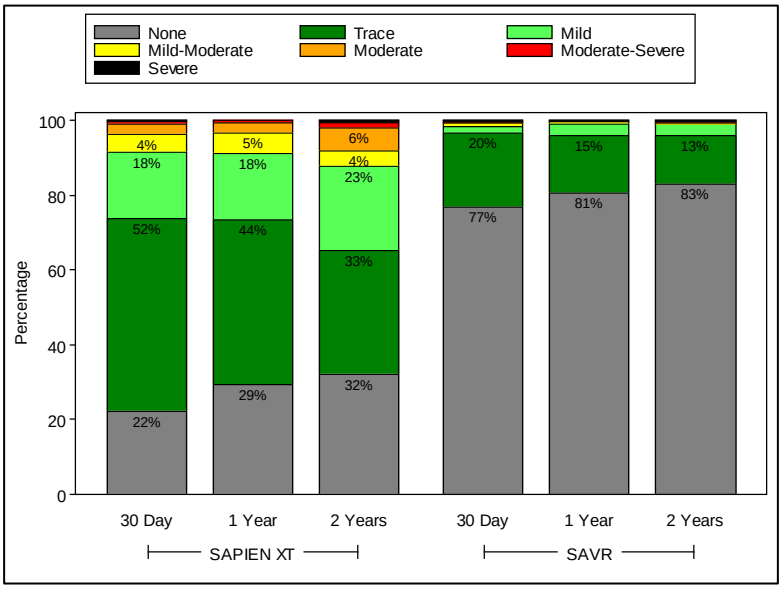


Figure 15: Aortic Paravalvular Leak (VI Population)



NYHA

The NYHA classifications by visit are presented in Figure 16. In the SAPIEN XT AT population, 78% of the patients were in NYHA Class III or IV at baseline, which reduced to 11% at 30 days, 8% at 1 year, and 10% at 2 years, while in the SAVR AT population, the percentage of patients in NYHA Class III or IV was 76% at baseline, 14% at 30 days, 7% at 1 year, and 7% at 2 years. A side-by-side comparison of the results by access approach is presented in Figure 17.

Figure 16: NYHA Class (AT Population)

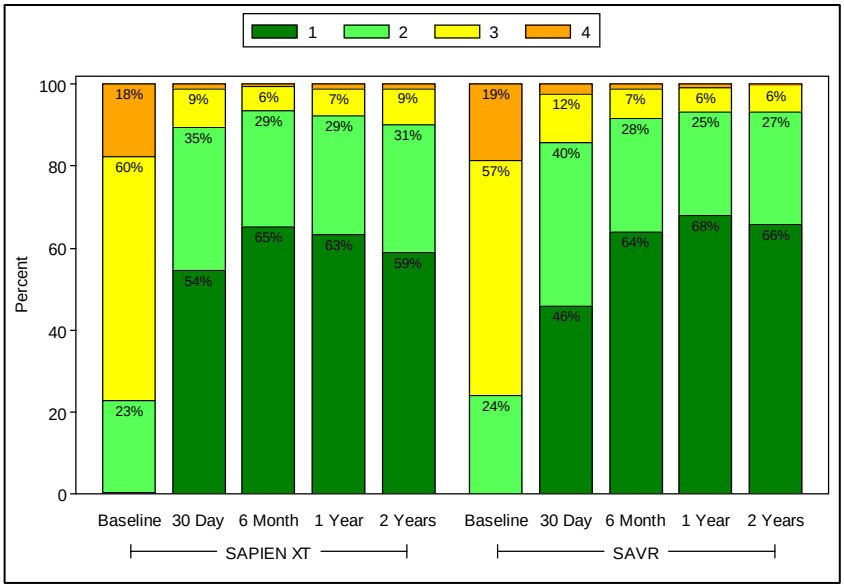
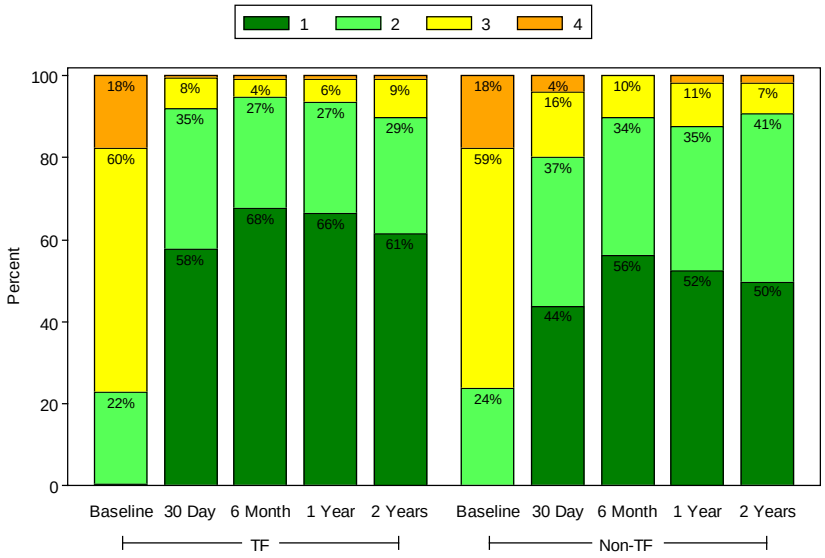


Figure 17: NYHA Class – TF versus non-TF Access (AT Population)



Length of Stay (LoS)

The results for LoS are presented in Table 12. Overall, the SAPIEN XT patients had shorter LoS' than the SAVR patients.

Table 12: Length of Stay (AT Population)

Length of Stay (days)*	SAPIEN XT			SAVR
	All	TF	Non-TF	
Overall	7.4±5.6	6.5±4.6	10.3±7.3	11.9±7.6
ICU	3.4±3.5	2.9±2.4	4.9±5.5	5.6±6.1

*Plus–minus values are means ± SD.

QoL

The QoL measurements using the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score are presented in Figure 18. Improvements were observed in all sub-scores at 30 days and were sustained at 1 and 2 years in the SAPIEN XT AT population. A side-by-side comparison of the results by access approach is presented in Figure 19. In general, improvements in the TF group were slightly larger compared to those observed in the non-TF group. Among the SAVR patients, improvements were observed in most sub-scores at 30 days and were sustained at 1 and 2 years, except decreases from baseline to 30 days in KCCQ physical limitations and social limitations.

Figure 18: KCCQ Clinical Summary Score (AT Population)

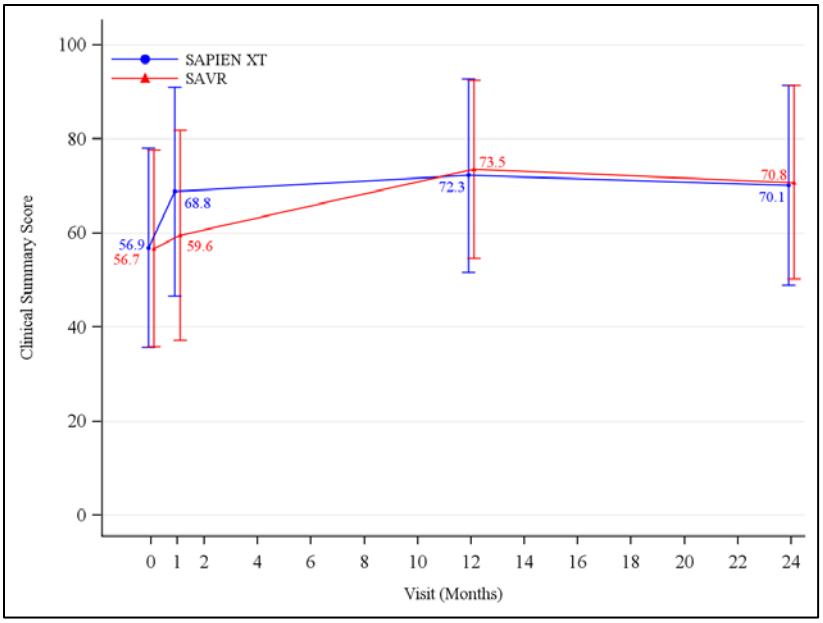
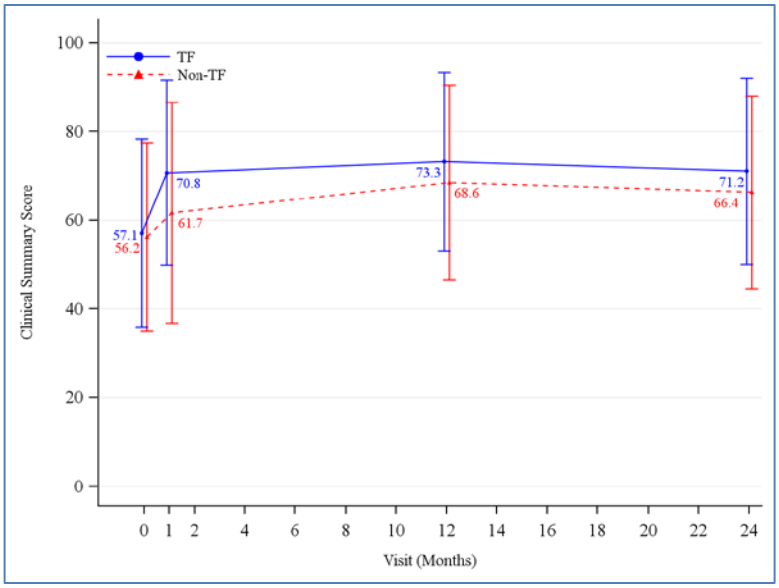


Figure 19: KCCQ Clinical Summary Score - TF versus non-TF Access (AT Population)



Additional QoL Instruments

QoL was also measured using the utility score of the EuroQoL (EQ-5D) measure and the SF-36 Health Status Questionnaire. The EQ-5D is a measure of self-reported health outcomes that is applicable to a wide range of health conditions and treatments. It consists of 2 parts: a descriptive system and a visual analogue scale (Part II). Part I of the scale consists of 5 single-item dimensions including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has a 3 point response scale designed to indicate the level of the problem. The overall EQ-5D score from Part I may be converted into a single index value (also known as utilities score) between 0.0 (i.e., death) and 1.0 (perfect health). SF-36 uses 36 questions to measure functional health and well-being from the patient's point of view and is generally reported in two (2) summary scores on a scale from 0 to 100 which evaluate physical (the Physical Summary Score) and mental (the Mental Summary Score) health, with higher scores representing better functional health and well-being. The results of the VAS and SF-36 measures are presented in Tables 13 and 14, respectively.

Table 13: EQ-5D Utilities Score (AT Population)

EQ-5D Utilities Score*	SAPIEN XT			SAVR
	All	TF	Non-TF	
Baseline	0.7±0.2	0.7±0.2	0.7±0.2	0.7±0.2
30 days	0.8±0.2	0.8±0.2	0.7±0.2	0.7±0.2
1 year	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2
2 years	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2

*Plus–minus values are means ± SD.

Table 14: SF-36 Health Status Questionnaire Score (AT Population)

SF-36 Health Status Questionnaire Score*	SAPIEN XT			SAVR
	All	TF	Non-TF	
Physical Component Score				
Baseline	36.1±8.9	36.3±9.0	35.6±8.7	35.9±8.7
30 days	40.0±9.3	41.0±9.2	36.5±8.6	36.1±8.0
1 year	40.6±9.8	40.8±9.9	39.8±9.2	41.0±9.9
2 years	39.4±9.8	39.8±9.8	37.8±9.4	39.1±10.0
Mental Component Score				
Baseline	48.8±11.3	48.7±11.2	49.0±11.7	47.7±11.8
30 days	50.4±11.7	51.4±11.2	46.7±12.6	45.5±12.8
1 year	52.2±10.9	52.4±10.5	51.4±11.9	51.6±10.8
2 years	51.5±10.9	51.5±10.8	51.7±11.3	51.6±10.8

*Plus–minus values are means ± SD.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conduction clinical studies covered by the regulation. The PIIA pivotal clinical study involved 411 investigators of which none were full-time or part-time employees of the sponsor including 28 investigators that had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: 28 investigators
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

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

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

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

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the clinical study, patients overall demonstrated clinically significant improvement in valve hemodynamics from baseline to 2 years. On average, the EOA increased from 0.7 cm^2 to 1.5 cm^2, the mean pressure gradient decreased from 45.0 mmHg to 10.8 mmHg, and the peak pressure gradient decreased from 79.0 mmHg to 21.3 mmHg in the SAPIEN XT patients. These trends were consistent with those observed in the SAVR patients. Specifically, the EOA at 2 years in the SAPIEN XT patients was found to be non-inferior to that in the SAVR patients with a margin of -0.2 (1.54 ± 0.44 m^2 vs. 1.40 ± 0.42 m^2). However, the study failed to reject the non-inferiority null hypothesis for difference in mean total AR at 2 years between SAPIEN XT and SAVR at a pre-specified margin of 0.25 (1.2 ± 1.0 vs. 0.5 ± 0.7).

The improvement in valve hemodynamics in the SAPIEN XT patients was further demonstrated through improvements in 6MWT distance from baseline to 2 years, NYHA classification and QoL. The 6MWT distance increased by 14.5 ± 128.7 m, which demonstrated superiority over SAVR. About 11%, 8%, and 10% of patients were in NYHA Class III or IV at 30 days, 1 year, and 2 years, respectively, as compared to 78% at baseline. The mean KCCQ Clinical Summary Score increased from 56.9 at baseline to 68.8 at 30 days, 73.5 at 1 year, and 70.8 at 2 years. SAPIEN XT was also found to be non-inferior to SAVR in NYHA at 2 years (1.5 ± 0.7 vs. 1.4 ± 0.6), DAOH to 2 years (637.5 ± 203.2 days vs. 619.0 ± 233.1 days), and 6MWT distance at 2 years (203.2 ± 132.4 m vs. 209.8 ± 153.5 m).

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 nonclinical laboratory (e.g., biocompatibility, hydrodynamic performance, durability, and structural integrity) and animal studies demonstrated that this device is suitable for long-term implant.

The pivotal clinical study has shown that TAVR with the SAPIEN XT THV was non-inferior to SAVR with a relative risk non-inferiority margin of 1.2 in the composite event rate of all-cause death or disabling stroke at 2 years (K-M estimates: 19.3% for

SAPIEN XT vs. 21.1% for SAVR; *p*=0.0014; ITT population). As such, the study met the pre-specified primary endpoint. The K-M estimated rates of all-cause death and disabling stroke at 2 years were clinically comparable between SAPIEN XT and SAVR (16.7% vs. 18.0% for all-cause death; 6.2% vs. 6.4% for disabling stroke).

C. Benefit-Risk Determination

The probable benefits of the SAPIEN XT THV are based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefits include improved valve hemodynamic performance, improved functional status as measured by NYHA classification and 6MWT distance, and improved QoL at 2 years, as compared to baseline.

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

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device. However, since TAVR with the SAPIEN XT THV provides a less invasive alternative to SAVR, FDA believes that many patients would prefer the TAVR therapy.

In conclusion, given the available information above, the data support that for patients with severe native aortic stenosis who are at intermediate or greater risk for open aortic valve replacement surgery, 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. The preclinical and clinical studies conducted on the SAPIEN XT THV provide reasonable assurance that the device is safe and effective for the replacement of native aortic valves in symptomatic severe aortic stenosis patients who are deemed to be at intermediate or greater surgical risk, defined as having a predicted risk of surgical mortality of ≥ 3% at 30 days, based on the STS risk score and other clinical co-morbidities unmeasured by the STS risk calculator (note that this risk level is lower than that defined in the inclusion criteria of the PIIA trial so that most patients with advanced age (e.g., ≥ 85 years old) could consider TAVR as an alternative therapy).

XIII. CDRH DECISION

CDRH issued an approval order on August 18, 2016. The final conditions of approval cited in the approval order are described below.

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

1. ***ODE Lead Post-Approval Study (Continued follow-up of the premarket cohort)***: The study will consist of all living subjects who were enrolled under the IDE in the PIIA Cohort. The objective of this study is to characterize the clinical outcomes annually through 10 years post-procedure. The key safety and effectiveness endpoints include all-cause mortality, all stroke, TIA, myocardial infarction, new permanent pacemaker, new-onset atrial fibrillation, rehospitalization from symptoms of aortic stenosis and/or complications of the valve procedure, improvement per NYHA Class, improvement per KCCQ and EQ-5D, valve performance and durability, and aortic valve re-intervention.

2. ***OSB Lead Surveillance***: The applicant is required to actively participate as a stakeholder and support the operations of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry (TVTR) to ensure that FDA surveillance occurs for the SAPIEN XT THV device over the next 5 years. This surveillance will monitor the following: 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, myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months; (3) neurological complications (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 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.

XV. REFERENCES

[1] Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol 2011; 57(3):253-69.