SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Aortic valve, prosthesis, percutaneously delivered
Device Trade Name:	Edwards SAPIEN 3™ Transcatheter Heart Valve, model 9600TFX, 20, 23, 26, and 29 mm, and accessories (Edwards Commander™ delivery system, models 9600LDS20, 9600LDS23, 9600LDS26, and 9600LDS29, with crimp stopper and Qualcrimp crimping accessory; and Edwards crimper, model 9600CR)
Device Procode:	NPT
Applicant Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P140031/S010
Date of FDA Notice of Approval:	August 18, 2016
Priority Review:	Granted priority review status on March 30, 2016 because the availability of the device is in the best interest of the patients

The original PMA P140031 was approved on June 17, 2015 and is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days). The SSED to support the indication is available on the CDRH website (http://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031b.pdf) and is incorporated by reference herein. The current supplement was submitted to expand the indication for the Edwards SAPIEN 3 Transcatheter Heart Valve to include patients with intermediate surgical risk for aortic valve replacement.

II. INDICATIONS FOR USE

The Edwards SAPIEN 3 Transcatheter Heart Valve (THV), model 9600TFX, and accessories are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at 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 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.

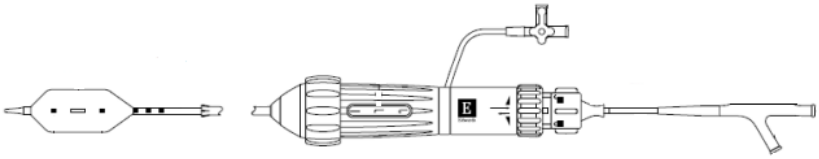
V. DEVICE DESCRIPTION

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

Figure 1: SAPIEN 3 Transcatheter Heart Valve

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

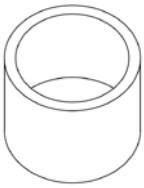
Figure 2: Edwards Commander Delivery System



Note that the SAPIEN 3 THV can also be delivered via the transapical or transaortic access route using the Edwards Certitude delivery system, which was used in the clinical trial but is not yet ready for commercial use in the U.S. at the present time.

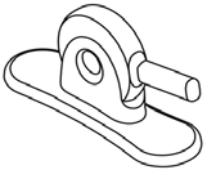
The Qualcrimp crimping accessory, as shown in Figure 3, is a non-patient contacting device that is placed around the Edwards SAPIEN 3 THV to protect the leaflets during the crimping process. It is manufactured of tubular polyester polyurethane foam and laminated cylindrically on both the inner and outer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

Figure 3: Qualcrimp Crimping Accessory



The Edwards Crimper, as shown in Figure 4, 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 4: 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 3 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, 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/pdf14/P140031b.pdf).

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study in the U.S. to establish a reasonable assurance of safety and effectiveness of transcatheter aortic valve replacement (TAVR) with the Edwards SAPIEN 3 THV in patients with severe native calcific aortic stenosis who are judged by a heart team to be at intermediate risk for open surgical therapy under IDE G090216 (entitled the "PARTNER II" trial), specifically under the PIIS3i cohort. The data from the PIIS3i cohort were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The PIIS3i cohort of the PARTNER II trial was a single arm, non-randomized, historical-controlled study to compare TAVR with the Edwards SAPIEN 3 THV system to the SAVR arm from the previous PARTNER II Trial Cohort A (PIIA-SAVR; see the SSED

for P130009/S057 for details). The valve sizes used in the PIIS3i study included the 20, 23, 26, and 29 mm sizes.

Patients in PIIS3i were treated between February 2014 and September 2014. Patients in PIIA-SAVR were treated between January 2012 and November 2013. The database reflected data collected through December 10, 2015 and included 1,078 patients in PIIS3i enrolled at 51 investigational sites in the U.S. and 1,021 patients in PIIA-SAVR enrolled at 57 investigational sites in the U.S.

The PIIS3i 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-2) definitions[1], with the following exceptions:

- Prosthetic valve dysfunction was adjudicated per VARC-1.
- Aortic valve reintervention was adjudicated per the protocol definition.
- Rehospitalization for symptoms of aortic stenosis and/or complications of the valve procedure were adjudicated using the protocol and VARC-2 definitions as guidelines.

The events in the PIIA-SAVR cohort were adjudicated by the CEC in accordance with the pre-specified, primarily VARC-1 definitions, with the following exceptions:

- Acute kidney injury (AKI) was adjudicated with a modified VARC-1 definition in which the CEC applied the 72-hour staging window to any AKI event that occurred within 30 days.
- Aortic valve reintervention were adjudicated per the protocol definition.
- Rehospitalization for symptoms of aortic stenosis and/or complications of the valve procedure were adjudicated using the protocol and VARC-1 as guidelines.
- Bleeding events were adjudicated irrespective of whether there was an identifiable, overt source of bleeding.

An electrocardiogram (ECG) core laboratory was used for independent analysis of rhythm, an echocardiographic core laboratory for echocardiograms, and a computerized tomography (CT) core laboratory for baseline CTs for annulus dimensions.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the PIIS3i study was limited to patients who met the following inclusion criteria:

   - Assessment of intermediate surgical risk defined as Society of Thoracic Surgeons (STS) score of 4%-8% or Heart Team assessment of intermediate risk factors.

- Senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient > 40 mmHg or jet velocity > 4.0 m/s and an initial aortic valve area (AVA) of < 0.80 cm^2 or indexed effective orifice area (EOA) < 0.5 cm^2/m^2. Qualifying echo was required to be within 60 days of the date of the procedure.
- Aortic valve annulus area range (273 mm^2-680 mm^2) per 3D imaging (echo, CT, or MRI).
- Symptomatic from 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 Heart Team agreed (a priori) on treatment strategy for concomitant coronary disease (if present).
- The study patient or the study patient's legal representative was informed of the nature of the study, agreed to its provisions and provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.
- The study patient agreed to comply with all required post-procedure follow-up visits including annual visits through 5 years and analysis close date visits, which were to be conducted as a phone follow-up.

Patients were <u>not</u> permitted to enroll in the PIIS3i 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) ≤ 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 ≥ twice normal in the presence of MB elevation and/or troponin level elevation (World Health Organization [WHO] definition)).
- Aortic valve was a congenital unicuspid or congenital bicuspid valve, or was non-calcified.
- Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
- Pre-existing mechanical or bioprosthetic valve in any position.
- 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 or implantable cardioverter defibrillator (ICD) was not considered exclusionary.

- 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 (white blood cells [WBC] < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), thrombocytopenia (Plt < 50,000 cell/mL).
- Hypertrophic cardiomyopathy with or without obstruction.
- Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of screening evaluation.
- Need for emergency surgery for any reason.
- Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20%.
- Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
- Active upper gastro-intestinal (GI) bleeding within 3 months (90 days) prior to procedure.
- A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.
- Native aortic annulus size < 16 mm or > 28 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 carcinoma, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease.
- Expectation that patient would not improve despite treatment of aortic stenosis.
- Significant aortic disease, including marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta. (Transfemoral)
- Iliofemoral vessel characteristics that would preclude safe placement of 14F or 16F introducer sheath such as severe obstructive calcification, severe tortuosity or minimum average vessel size less than 5.5 mm. (Transfemoral)
- 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.
- Known enrollment in the PARTNER I Trial.
- Active bacterial endocarditis within 6 months (180 days) of procedure.

2. Follow-up Schedule

Follow-up periods were discharge, 30 days, 6 months, and 12 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, all stroke, or aortic insufficiency (AI) ≥ moderate at 1 year. Death and stroke were evaluated by the CEC, and AI was assessed by the echocardiography core laboratory. Events occurring on day 365 or earlier were included in the evaluation. The primary hypothesis was as follows:

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

where P_T denotes the event proportion in the test arm, and P_C denotes the event proportion in the control arm. The non-inferiority test was performed at a one-sided α level of 0.05 and adjusted for propensity quintiles.

There were five (5) pre-specified hypothesis-driven secondary endpoints:

1) Composite event of all-cause death, all stroke, life-threatening (disabling)/major bleeding, and major vascular and access complication at 30 days
2) Major vascular and access complications through 30 days
3) Life-threatening (disabling)/major bleeding through 30 days
4) All-cause death through 30 days
5) All stroke through 30 days.

The hypothesis for each of the above secondary endpoint was as follows:

$$H_0: P_T - P_C \geq \Delta$$
$$H_A: P_T - P_C < \Delta$$

where P_T and P_C denote the event proportions in the test and control arms, respectively, and Δ denotes the non-inferiority margin. The Δ values were chosen to be 7.5%, 5.0%, 5.0%, 2.5%, and 2.5% for the above five (5) secondary endpoints, respectively. The non-inferiority tests were performed at a one-sided α level of 0.05 and were adjusted for the stratification of propensity quintiles first and then for multiplicity.

B. Accountability of the PMA Cohort

At the time of database lock, of the 1078 patients enrolled in the PMA study (PIIS3i), 99.2% (1069) patients are available for analysis at the completion of the study, the 1-year post-operative visit. Table 1 presents patient accountability in the PIIS3i and PIIA-SAVR cohorts. Of the 1,074 eligible patients (Eligible Patient or EP Population) in PIIS3i, 1,069 were successfully implanted with a SAPIEN 3 THV and constitute the PIIS3i Valve Implant (VI) population. Among the VI population, 943 patients were implanted via the transfemoral (TF) access route, and 126 patients via a non-transfemoral (non-TF; mainly transapical and transaortic) access route. Of the 938 eligible patients in the PIIA-SAVR cohort, 936 were successfully implanted with a surgical valve and constitute the PIIA-SAVR VI population.

Table 1: Patient Accountability

	All Enrolled Patients	Eligible Patient (EP) Population*	Valve Implant (VI) Population†
SAPIEN 3	1078	1074	1069
TF	952	948	943
Non-TF	126	126	126
PIIA-SAVR	1021	938	936

*Eligible Patient (EP) Population consists of all enrolled patients who were determined eligible after screening, entered into the catheterization laboratory, and remained eligible to receive the assigned implant.

†Valve Implant (VI) Population is a subset of the EP Population who received the assigned valve, and retained the valve upon leaving the catheterization laboratory.

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, as summarized in Table 2 for the PIIS3i and PIIA-SAVR EP populations.

Table 2: Patient Demographics and Baseline Characteristics of the EP Population

Demographics & Characteristics*	SAPIEN 3			PIIA-SAVR (N = 938)
	Overall (N = 1074)	TF Only (N = 948)	Non-TF Only (N = 126)	
Age - years	81.9±6.60	82.1±6.57	80.7±6.69	81.6±6.73
Male sex	662/1074 (61.6%)	577/948 (60.9%)	85/126 (67.5%)	514/938 (54.8%)
Society of Thoracic Surgeons (STS) score	5.3±1.29	5.3±1.29	5.6±1.28	5.8±1.92
New York Heart Association (NYHA) class				

Demographics & Characteristics*	SAPIEN 3			PIIA-SAVR (N = 938)
	Overall (N = 1074)	TF Only (N = 948)	Non-TF Only (N = 126)	
I/II	294/1074 (27.4%)	262/948 (27.6%)	32/126 (25.4%)	225/937 (24.0%)
III/IV	780/1074 (72.6%)	686/948 (72.4%)	94/126 (74.6%)	712/937 (76.0%)
Coronary artery disease	748/1074 (69.6%)	652/948 (68.8%)	96/126 (76.2%)	623/938 (66.4%)
Previous myocardial infarction	172/1074 (16.0%)	133/948 (14.0%)	39/126 (31.0%)	166/938 (17.7%)
Previous intervention				
Coronary artery bypass grafting (CABG)	301/1074 (28.0%)	248/948 (26.2%)	53/126 (42.1%)	241/938 (25.7%)
Percutaneous coronary intervention (PCI)	344/1074 (32.0%)	299/948 (31.5%)	45/126 (35.7%)	254/938 (27.1%)
Prior aortic valvuloplasty	55/1074 (5.1%)	51/948 (5.4%)	4/126 (3.2%)	45/938 (4.8%)
Cerebral vascular accident (CVA)	97/1074 (9.0%)	81/948 (8.5%)	16/126 (12.7%)	96/938 (10.2%)
Peripheral vascular disease	304/1074 (28.3%)	231/948 (24.4%)	73/126 (57.9%)	301/938 (32.1%)
Chronic obstructive pulmonary disease (COPD)				
Any	321/1072 (29.9%)	270/946 (28.5%)	51/126 (40.5%)	279/932 (29.9%)
Oxygen-dependent	53/1067 (5.0%)	46/942 (4.9%)	7/125 (5.6%)	26/925 (2.8%)
Atrial fibrillation	385/1074 (35.8%)	342/948 (36.1%)	43/126 (34.1%)	326/938 (34.8%)
Permanent pacemaker	142/1074 (13.2%)	121/948 (12.8%)	21/126 (16.7%)	113/938 (12.0%)
Severe pulmonary hypertension	25/1074 (2.3%)	19/948 (2.0%)	6/126 (4.8%)	N/A
Frailty	92/1074 (8.6%)	86/948 (9.1%)	6/126 (4.8%)	15/938 (1.6%)
Porcelain aorta	1/1074 (0.1%)	1/948 (0.1%)	0/126 (0.0%)	0/938 (0.0%)
Chest deformities that preclude an open chest procedure	1/1074 (0.1%)	1/948 (0.1%)	0/126 (0.0%)	0/938 (0.0%)

Demographics & Characteristics*	SAPIEN 3			PIIA-SAVR (N = 938)
	Overall (N = 1074)	TF Only (N = 948)	Non-TF Only (N = 126)	
Cirrhosis	4/1074 (0.4%)	4/948 (0.4%)	0/126 (0.0%)	4/938 (0.4%)
Echocardiographic findings (Valve Implant Population)				
Effective orifice area (EOA; cm^2)	0.7±0.17	0.7±0.16	0.7±0.18	0.7±0.20
Mean aortic-valve gradient - mmHg	46.1±12.63	46.1±12.66	45.8±12.47	44.7±12.55
Mean left ventricular ejection fraction (LVEF; %)	58.5±13.36	58.8±13.24	56.0±14.05	55.4±11.75
Moderate or severe mitral regurgitation	91/1033 (8.8%)	87/909 (9.6%)	4/124 (3.2%)	153/841 (18.2%)

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

D. Safety and Effectiveness Results

1. Primary Endpoint

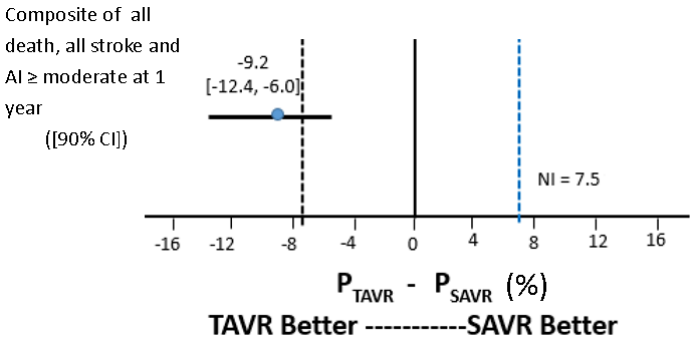
The primary endpoint was a composite of all-cause death, stroke, and AI ≥ moderate at 1 year. The weighted proportion difference of the primary endpoint was -9.2% (90% CI: [-12.4%, -6.0%]) using the average treatment effect on the treated (ATT) method[2], as shown in Table 3 and Figure 5. Since the upper limit of the CI was < 7.5%, non–inferiority was met.

Table 3: Primary Endpoint Non-Inferiority Test (VI Population)

	Observed Event Rate		Propensity Score Quintile Pooled Proportion Difference (ATT Method*) [90% CI]†	Margin	Conclusion for Non-Inferiority Test
	SAPIEN 3 (N=1069)	PIIA-SAVR (N=936)			
Composite of all-cause death, all stroke and aortic insufficiency (AI) ≥ moderate at 1 year	13.0%	23.2%	-9.2% [-12.4%, -6.0%]	7.5%	Pass

*ATT: average treatment effect on the treated
†Two-sided 90% Wald-type confidence interval

Figure 5: Forest Plot – Composite of All Death, All Stroke and AI ≥ Moderate (VI Population)



The Kaplan-Meier (K-M) estimates for all-cause death and all stroke at 1 year for the PIIS3i cohort and the PIIA-SAVR cohort are provided in Table 4 as well as Figures 6 and 7, respectively.

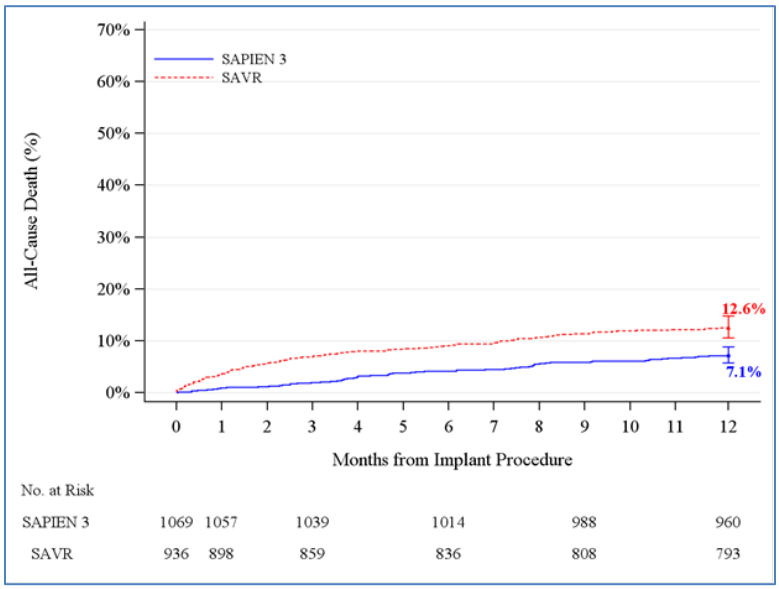
Table 4: All-Cause Death and All Stroke at 1 Year (VI Population)

	SAPIEN 3 (N= 1069)			PIIA-SAVR (N= 936)			Propensity Score Quintile Pooled Proportion Difference (ATT Method†)
Endpoints	Observed Event Rate	Kaplan-Meier Event Rate*		Observed Event Rate	Kaplan-Meier Event Rate*		
		Point Estimate	Standard Error		Point Estimate	Standard Error	
All-cause death at 1 year	7.0%	7.1%	0.79%	12.4%	12.6%	1.09%	-5.2%
All stroke at 1 year	4.5%	4.6%	0.65%	7.9%	8.1%	0.91%	-3.5%

*Kaplan-Meier estimates were calculated at 365 days and included only the first event for each patient. Events occurring after 365 days were not included in this analysis.

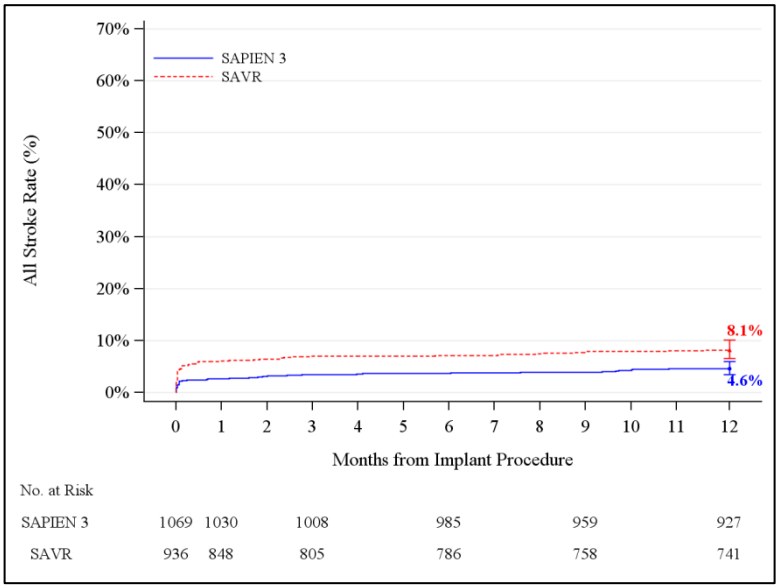
†ATT: average treatment effect on the treated

Figure 6: All-Cause Death through 1 Year (VI Population)



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

Figure 7: All Stroke through 1 Year (VI Population)



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

The proportion of patients with AI ≥ moderate at 1 year was 1.6% for the PIIS3i cohort and 0.3% for the PIIA-SAVR cohort, as shown in Table 5.

Table 5: Aortic Insufficiency (AI) ≥ Moderate at 1 Year (VI Population)

	Observed Event Rate		Propensity Score Quintile Pooled Proportion Difference (ATT Method*)
	SAPIEN 3 (N= 1069)	PIIA-SAVR (N= 936)	
Aortic insufficiency (AI) ≥ moderate	1.6%	0.3%	1.2%

*ATT: average treatment effect on the treated

2. Secondary Endpoints

The secondary endpoints were examined in a pre-specified order adjusted for the propensity quintiles using the ATT method. Table 6 summarizes the statistical conclusions on the non-inferiority hypothesis testing of the five (5) secondary endpoints that were evaluated using a gatekeeping/hierarchical multiplicity adjustment procedure to control the overall type I error to 0.05. For each secondary endpoint, the upper limit of the confidence interval was less than the respective non-inferiority margin. Therefore, for each of the secondary endpoints for labeling, the SAPIEN 3 was non-inferior to SAVR.

Table 6: Secondary Endpoints for Labeling – Gatekeeping/Hierarchical Method (VI Population)

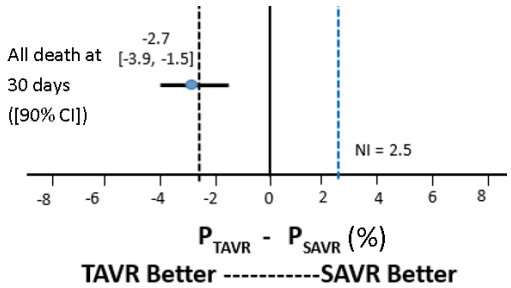
Pre-Specified Order for Gatekeeping/ Hierarchical Method	Endpoints	Observed Event Rate		Weighted Proportion Difference in Average Treatment Effect on the Treated [90% CI]*	Margin	Conclusion for Non-Inferiority Test
		SAPIEN 3 (N=1069)	PIIA-SAVR (N=936)			
No. 1	Composite of all-cause death, all stroke, life threatening (disabling)/ major bleeding and major vascular complication at 30 days	18.3%	79.4%	-60.5% [-63.5%, -57.4%]	7.5%	Pass

Pre-Specified Order for Gatekeeping/ Hierarchical Method	Endpoints	Observed Event Rate		Weighted Proportion Difference in Average Treatment Effect on the Treated [90% CI]*	Margin	Conclusion for Non-Inferiority Test
		SAPIEN 3 (N=1069)	PIIA-SAVR (N=936)			
No. 2	Major vascular and access complication through 30 days	5.8%	5.3%	0.3% [-1.5%, 2.0%]	5.0%	Pass
No. 3	Life threatening (disabling)/ major bleeding through 30 days	14.6%	78.2%	-63.2% [-66.2%, -60.2%]	5.0%	Pass
No. 4	All-cause death through 30 days	0.9%	3.7%	-2.7% [-3.9%, -1.5%]	2.5%	Pass
No. 5	All stroke through 30 days	2.6%	6.1%	-3.2% [-4.7%, -1.6%]	2.5%	Pass

*Two-sided 90% Wald-type confidence interval.

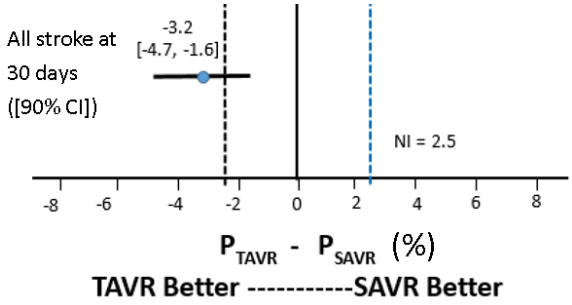
The forest plots for all-cause death and all stroke at 30 days are provided in Figures 8 and 9, respectively.

Figure 8: Forest Plot – All-Cause Death at 30 Days (VI Population)



Note: As part of a pre-specified hiearchy, the hypothesis for this endpoint was tested using a hierarchical gatekeeping approach. The confidence interval shown here was not adjusted for multiplicity per the gatekeeping approach.

Figure 9: Forest Plot – All Stroke at 30 Days (VI Population)



Note: As part of a pre-specified hiearchy, the hypothesis for this endpoint was tested using a hierarchical gatekeeping approach. The confidence interval shown here was not adjusted for multiplicity per the gatekeeping approach.

3. Adverse Events

The key CEC-adjudicated adverse events through 1 year for the EP population are presented in Table 7.

Table 7: CEC-Adjudicated Adverse Events through 1 Year (EP Population)

Event*	SAPIEN 3			PIIA-SAVR
	Overall	TF Only	Non-TF Only	
7 Days				
Acute kidney injury: Stage III	5/1074 (0.5%)	3/948 (0.3%)	2/126 (1.6%)	N/A
30 Days				
Death	12/1074 (1.1%)	10/948 (1.1%)	2/126 (1.6%)	35/938 (3.7%)
Cardiac death	10/1074 (0.9%)	9/948 (0.9%)	1/126 (0.8%)	26/938 (2.8%)
Non-cardiac death	2/1074 (0.2%)	1/948 (0.1%)	1/126 (0.8%)	9/938 (1.0%)
Stroke	29/1074 (2.7%)	24/948 (2.5%)	5/126 (4.0%)	57/938 (6.1%)
Major (disabling) stroke	11/1074 (1.0%)	7/948 (0.7%)	4/126 (3.2%)	41/938 (4.4%)
Minor (non-disabling) stroke	18/1074 (1.7%)	17/948 (1.8%)	1/126 (0.8%)	16/938 (1.7%)
Myocardial infarction	3/1074 (0.3%)	3/948 (0.3%)	0/126 (0.0%)	17/938 (1.8%)
Major vascular complication	65/1074 (6.1%)	60/948 (6.3%)	5/126 (4.0%)	50/938 (5.3%)

Event*	SAPIEN 3			PIIA-SAVR
	Overall	TF Only	Non-TF Only	
Life threatening (disabling) or major bleeding	159/1074 (14.8%)	112/948 (11.8%)	47/126 (37.3%)	733/938 (78.1%)
Aortic valve re-intervention	1/1074 (0.1%)	1/948 (0.1%)	0/126 (0.0%)	0/938 (0.0%)
Any endocarditis	2/1074 (0.2%)	2/948 (0.2%)	0/126 (0.0%)	0/938 (0.0%)
Rhythm disturbance requiring permanent pacemaker	108/1074 (10.1%)	99/948 (10.4%)	9/126 (7.1%)	68/938 (7.2%)
1 Year				
Death	79/1074 (7.4%)	61/948 (6.4%)	18/126 (14.3%)	117/938 (12.5%)
Cardiac death	47/1074 (4.4%)	37/948 (3.9%)	10/126 (7.9%)	70/938 (7.5%)
Non-cardiac death	32/1074 (3.0%)	24/948 (2.5%)	8/126 (6.3%)	47/938 (5.0%)
Stroke	49/1074 (4.6%)	40/948 (4.2%)	9/126 (7.1%)	74/938 (7.9%)
Major (disabling) stroke	24/1074 (2.2%)	16/948 (1.7%)	8/126 (6.3%)	53/938 (5.7%)
Minor (non-disabling) stroke	25/1074 (2.3%)	24/948 (2.5%)	1/126 (0.8%)	22/938 (2.3%)
Aortic valve re-intervention	6/1074 (0.6%)	6/948 (0.6%)	0/126 (0.0%)	4/938 (0.4%)
Any endocarditis	8/1074 (0.7%)	7/948 (0.7%)	1/126 (0.8%)	6/938 (0.6%)

*Categorical measures - n/total no. (%)

In addition, site-reported new-onset atrial fibrillation was 5.9% in the PIIS3i EP population and 29.2% in the PIIA-SAVR EP population.

Bleeding Rate

The bleeding rates utilizing the number of units transfused are presented in Table 8.

Table 8: Bleeding Rate Using Site-Reported Units Transfused (EP Population)

Event*	SAPIEN 3 (N = 1074)	PIIA-SAVR (N = 938)
Transfusion units ≥ 2 and < 4	47/1074 (4.4%)	184/938 (19.6%)
Transfusion units ≥ 4	18/1074 (1.7%)	218/938 (23.2%)

*Site-reported transfusion at day 0 or day 1; Categorical measures - n/total no. (%)

4. Other Results

Procedural Information

In the PIIS3i EP population, the mean duration in the catheterization laboratory was 187.3±53.2 minutes, the mean total procedure time was 84.2±40.7 minutes, and the mean total anesthesia time was 186.9±61.1 minutes, all of which were slightly shorter in the TF group. General anesthesia was used in the vast majority of cases; 18.9% of the TF patients had conscious sedation. Correct positioning of the valve was achieved in 99.3% of the patients. Four (4) patients (0.4%, all TF patients) were implanted with a second valve. One (1) patient (0.1%) experienced valve embolization and two (2) patients (0.2%) experienced annular rupture.

In the PIIA-SAVR EP population, the mean duration in the operating room was 333.2±96.4 minutes, the mean total procedure time was 237.5±86.6 minutes, and the mean anesthesia time was 333.5±108.4 minutes. General anesthesia was used in all patients.

Valve Performance

The measurements of EOA, mean gradient, peak gradient, total aortic regurgitation (AR), and aortic paravalvular leak (PVL) are presented in Figures 10-14. The increase in EOA and decrease in gradient were sustained at 1 year. In PIIS3i, the proportion of patients with total AR ≥ moderate was 6.2% at baseline, 3.9% at 30 days, and 1.6% at 1 year, while in PIIA-SAVR, the proportion of patients with total AR ≥ moderate was 12.0% at baseline, 0.7% at 30 days, and 0.3% at 1 year. The proportion of patients with aortic PVL ≥ moderate was 3.8% at 30 days and 1.5% at 1 year in PIIS3i, as compared to 0.5% at 30 days and 0.3% at 1 year in PIIA-SAVR**.**

Figure 10: Effective Orifice Area (VI Population)

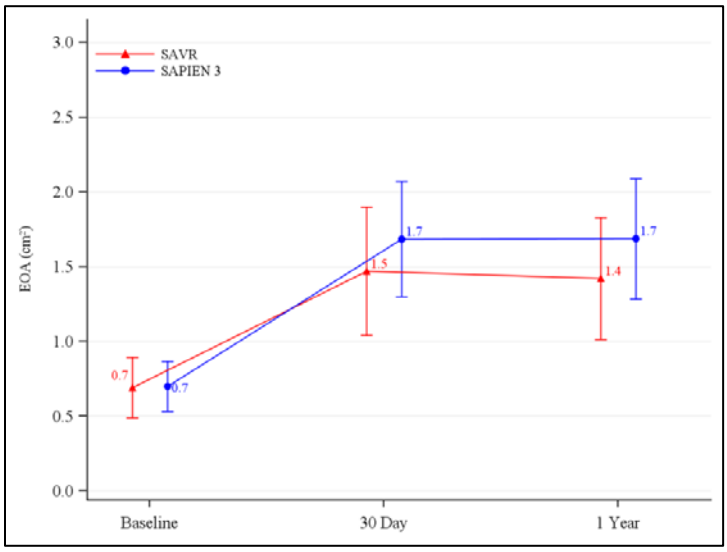


Figure 11: Mean Gradient (VI Population)

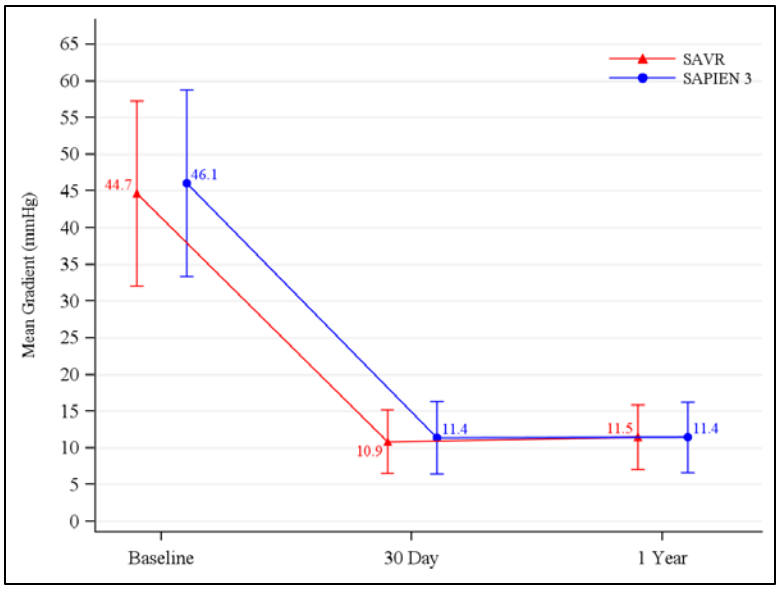


Figure 12: Peak Gradient (VI Population)

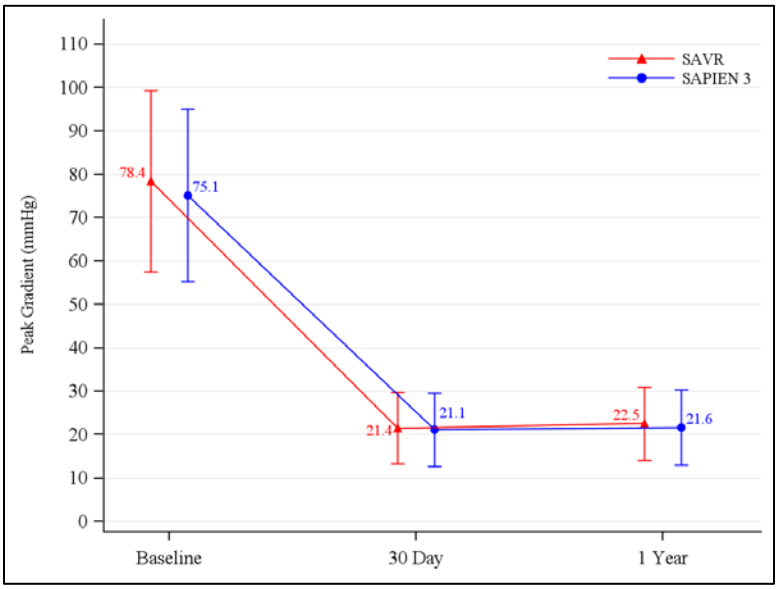


Figure 13: Total Aortic Regurgitation (VI Population)

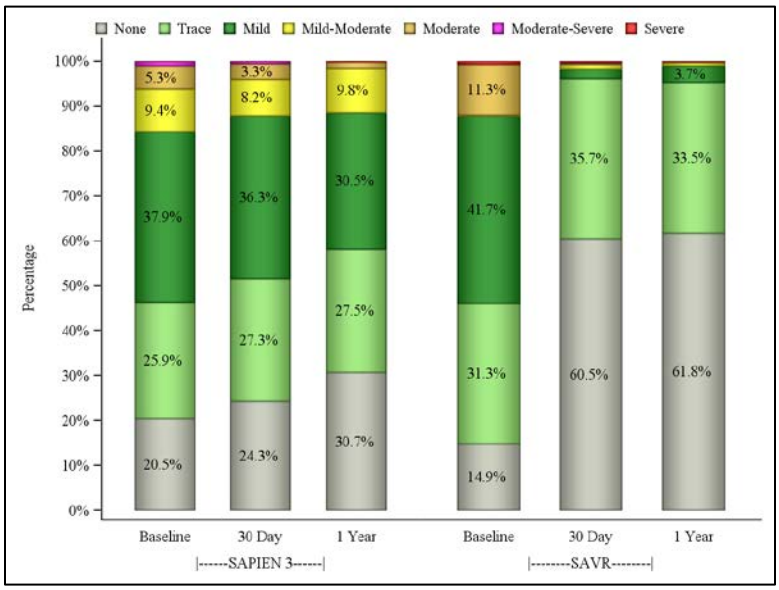
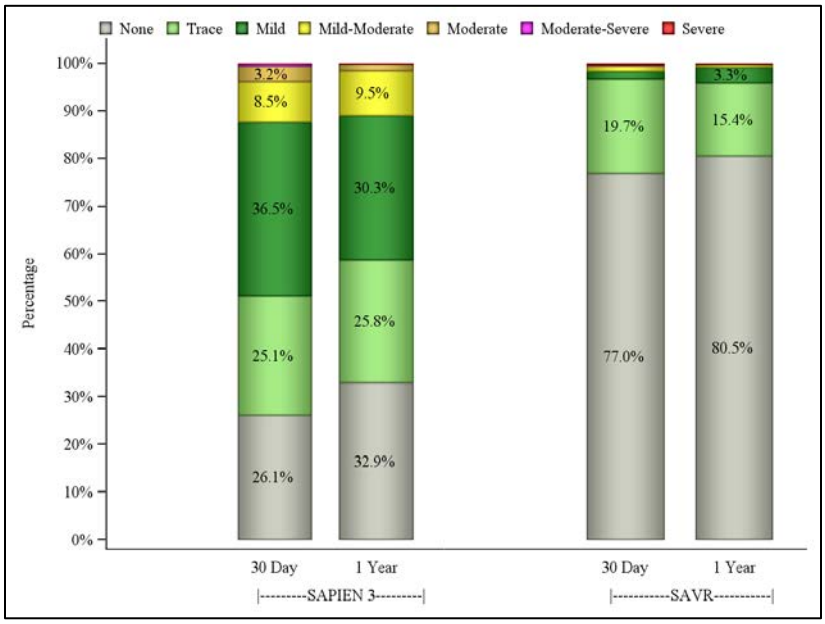


Figure 14: Aortic Paravalvular Leak (VI Population)



NYHA

The NYHA classifications by visit are presented in Figure 15. In PIIS3i, 72.6% of the patients were in NYHA Class III or IV at baseline, which reduced to 6.3% at 30 days and 6.7% at 1 year, while in PIIA-SAVR, the percentage of patients in NYHA Class III or IV was 76.0% at baseline, 13.6% at 30 days, and 6.7% at 1 year. A side-by-side comparison of the results by access approach is presented in Figure 16.

Figure 15: NYHA Class by Visit (EP Population)

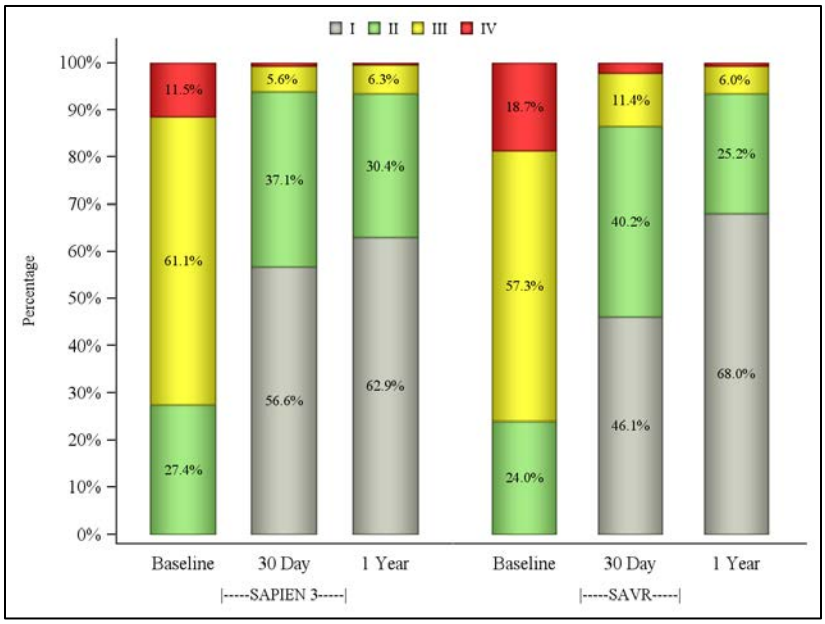
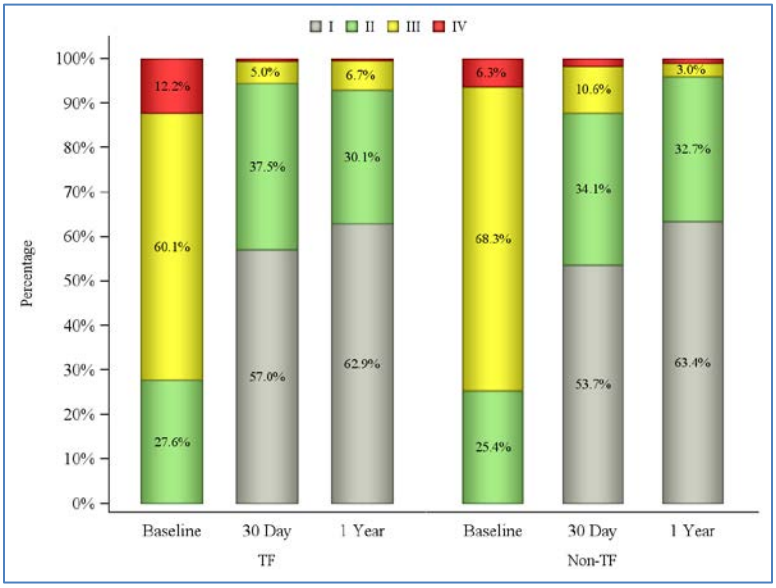


Figure 16: NYHA Class by Visit – TF versus non-TF Access (EP Population)



Six-Minute Walk Test (6MWT)

The improvements in mean 6MWT distance are presented in Table 9. The SAPIEN 3 patients had similar increase in mean 6MWT distance from baseline to 1 year as the PIIA-SAVR patients.

Table 9: 6MWT Distance (EP Population)

6MWT Distance (m)*	SAPIEN 3			PIIA-SAVR
	All	TF	Non-TF	
Baseline	193.9±118.1	194.1 ± 117.2	192.5 ± 125.5	179.3± 123.2
30 days	230.6±126.1	234.6 ± 123.6	199.0 ± 140.6	166.7 ± 126.4
1 year	227.7 ± 134.7	230.6 ± 133.6	202.8 ± 142.1	219.2 ± 133.8

*Plus–minus values are means ± SD.

Length of Stay (LoS)

The results for LoS are presented in Table 10. Overall, the SAPIEN 3 patients had shorter LoS than the PIIA-SAVR patients.

Table 10: Length of Stay (EP Population)

Length of Stay (days)*	SAPIEN 3			PIIA-SAVR
	All	TF	Non-TF	
Overall	5.5±5.7	5.0±5.2	9.3±7.7	11.9±7.6
ICU	2.7±3.0	2.5±2.6	4.2±4.9	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 17. Except for self-efficacy which showed a small improvement, moderate to large improvements were observed in all other subscores at 30 days and were sustained at 1 year in the PIIS3i EP population. A side-by-side comparison of the results by access approach is presented in Figure 18. In general, improvements in the TF group were slightly larger as compared to those observed in the Non-TF group.

Figure 17: KCCQ Clinical Summary Score (EP Population)

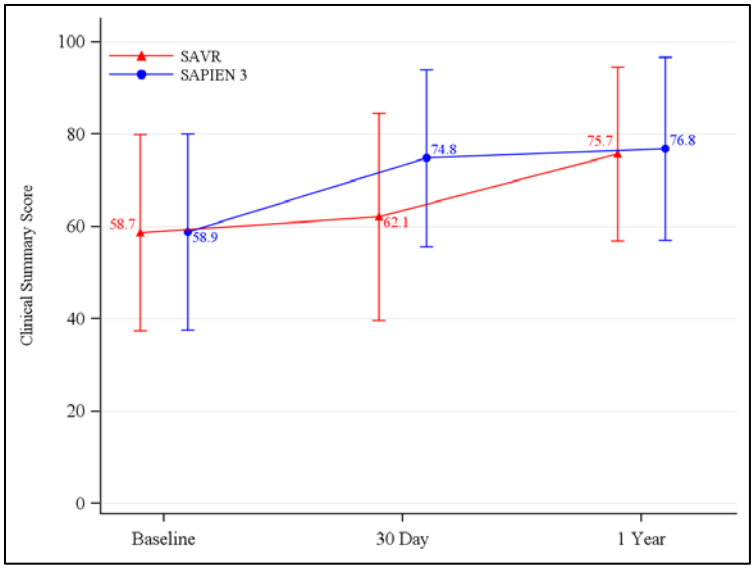
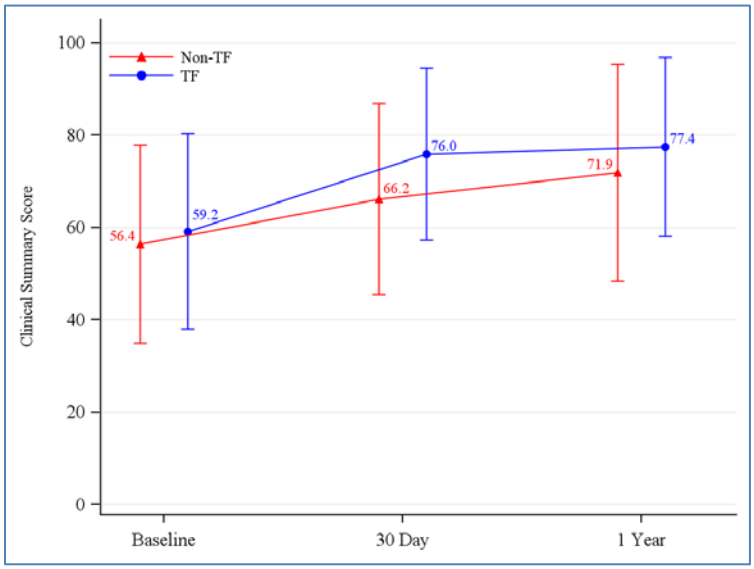


Figure 18: KCCQ Clinical Summary Score - TF versus non-TF Access (EP Population)



Additional QoL Instruments

QoL was also measured using the visual analog scale (VAS) of the EuroQoL (EQ-5D) measure and the SF-36 Health Status Questionnaire. The VAS is a self-assessment in which patients rate their well-being on a scale from 0 to 100 where 0 is the worst state they can imagine and 100 is the best state. 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 11 and 12, respectively.

Table 11: EQ-5D Visual Analog Scale (EP Population)

EQ-5D Visual Analog Scale*	SAPIEN 3			PIIA-SAVR
	All	TF	Non-TF	
Baseline	60.3 ± 20.0	61.0 ± 19.8	55.1 ± 20.7	59.5 ± 20.5
30 days	74.0 ± 16.6	74.8 ± 16.6	68.5 ± 16.2	67.2 ± 19.5
1 year	74.4 ± 17.2	74.7 ± 17.1	71.8 ± 17.8	74.3 ± 16.7

*Plus–minus values are means ± SD.

Table 12: SF-36 Health Status Questionnaire Score (EP Population)

SF-36 Health Status Questionnaire Score*	SAPIEN 3			PIIA-SAVR
	All	TF	Non-TF	
Physical Component Score				
Baseline	34.7±9.1	35.0±9.1	33.1±8.5	34.3±9.0
30 days	39.7±9.8	40.3±9.7	34.8±9.2	34.5±8.4
1 year	40.0±10.3	40.4±10.2	37.0±10.8	39.5±10.4
Mental Component Score				
Baseline	48.0±11.8	48.1±11.8	47.0±12.3	48.0±12.3
30 days	51.8±10.6	52.3±10.4	47.8±11.3	45.5±13.3
1 year	52.5±10.7	52.7±10.8	50.7±10.1	52.0±11.3

*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 PIIS3i pivotal clinical study involved 410 investigators of which none were full-time or part-time employees of the sponsor and 26 investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f), as 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: 26 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, the subjects overall demonstrated clinically significant improvement in valve hemodynamics from baseline to 1 year. On average, the EOA increased from 0.7 cm^2 to 1.7 cm^2, the mean pressure gradient decreased from 46.1 mmHg to 11.4 mmHg, and the peak pressure gradient decreased from 75.1 mmHg to 21.6 mmHg. The trends were consistent with those observed in PIIA-SAVR.

The improvement in valve hemodynamics in the SAPIEN 3 patients was further demonstrated through improvements in 6MWT distance, NYHA classification and QoL. On average, the 6MWT distance increased from 193.7 m to 227.4 m. About 6.3% and 6.7% of patients were in NYHA Class III or IV at 30 days and 1 year, respectively, as compared to 72.6% at baseline. The mean KCCQ Clinical Summary Score increased from 58.9 at baseline to 76.8 at 1 year.

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 observed composite event rate of all-cause mortality, all stroke, and AI ≥ moderate at 1 year (i.e., the primary endpoint) was 13.0% in the SAPIEN 3 cohort (test arm) and 23.2% in the PIIA-SAVR cohort (historical control arm). The weighted difference in the primary endpoint event rate between SAPIEN 3 and PIIA-SAVR was -9.2% with an upper limit of the 90% confidence interval of -6.0%, which was lower than the pre-specified non-inferiority margin of 7.5%. As such, the pivotal clinical study met the pre-specified primary endpoint. In addition, the difference in the primary endpoint event rate between SAPIEN 3 and PIIA-SAVR appeared to be clinically significant. The weighted differences in the rates of 1-year all-cause death, all stroke, and AI ≥ moderate between SAPIEN 3 and PIIA-SAVR were -5.2%, -3.5%, 1.2%, respectively.

At 30 days, SAPIEN 3 was found to be non-inferior to PIIA-SAVR in the composite event of all-cause death, all stroke, life-threatening (disabling)/major bleeding, or major vascular and access complication (difference = -60.5%); major vascular and access complications (difference = 0.3%); life-threatening (disabling)/major bleeding (difference = -63.2%); all-cause death (difference = -2.7%); and all stroke (difference = -3.2%). The point estimates of differences in 30-day all-death rate (-2.7%) and all stroke rate (-3.2%) suggest that the rates were lower in the SAPIEN 3 cohort as compared to the PIIA-SAVR cohort.

Of note is that the rate of conduction disturbance requiring permanent pacemaker following implantation of the SAPIEN 3 THV (10.1%) was clinically higher than those reported for SAPIEN THV (3.4-5.9%) and SAPIEN XT THV (6.7%).

C. Benefit-Risk Determination

The probable benefits of the SAPIEN 3 THV are based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefits include improved valve hemodynamic performance, improved functional status as measured by NYHA classification and 6MWT distance, and improved QoL at 1 year, as compared to baseline.

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

Considering the overall benefit/risk profile of TAVR with the SAPIEN 3 THV versus SAVR in the intermediate risk patients, the meaningful differences included clinically lower rates of all-cause death, all stroke, and life-threatening (disabling)/major bleeding, but higher rates of AI ≥ moderate and conduction disturbance requiring permanent pacemaker implantation in the SAPIEN 3 patients than in the SAVR patients.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device. However, since TAVR with the SAPIEN 3 THV provides a less invasive alternative to SAVR, FDA believes 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 3 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 PIIS3i 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 PIIS3i 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, transient ischemic attack (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 (from baseline), improvement per KCCQ, 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 3 THV device over the next 5 years. This

surveillance will monitor the following: (1) device success (intra-procedure); (2) all-cause mortality, all stroke, life-threatening/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 death, 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] Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). Eur J Cardiothorac Surg 2012; 42:S45-60.

[2] Imbens G. W. (2004) Nonparametric Estimation of Average Treatment Effects under Exogeneity: A Review. The Review of Economics and Statistics, February 2004, 86(1):4–29.