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 System
	Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System
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/S085
Date of FDA Notice of Approval:	August 16, 2019

The original PMA of the Edwards SAPIEN 3 Transcatheter Heart Valve (THV) System, P140031, was first approved on June 17, 2015, and the indication was later expanded in Panel Track PMA Supplement P140031/S010 on August 18, 2016, to include patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator). The indication was further expanded in PMA Supplement P140031/S028 on June 5, 2017 to include patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic or mitral valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the STS risk score and other clinical co-morbidities unmeasured by the STS risk calculator). The SSEDs to support the indication are available on the following FDA websites and are incorporated by reference herein:

- https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031b.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S010b.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S028b.pdf

The SAPIEN 3 Ultra THV System is a design iteration of the SAPIEN 3 THV System and was approved in P140031/S074 on December 28, 2018.

The current supplement was submitted to expand the indications for use of the Edwards SAPIEN 3 THV System and SAPIEN 3 Ultra THV System to include patients with severe symptomatic native calcific aortic stenosis who are deemed to be at low risk for surgical aortic valve replacement (SAVR).

II. INDICATIONS FOR USE

The Edwards SAPIEN 3 Transcatheter Heart Valve System and Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System 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 appropriate for the transcatheter heart valve replacement therapy.

III. CONTRAINDICATIONS

The Edwards SAPIEN 3 THV System and Edwards SAPIEN 3 Ultra THV System 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 3 THV System and Edwards SAPIEN 3 Ultra THV System labeling.

V. DEVICE DESCRIPTION

The Edwards SAPIEN 3 THV (model 9600TFX, 20, 23, 26, and 29 mm), as shown in Figure 1, is comprised of a balloon-expandable, radiopaque, cobalt-chromium (MP35N) frame, a trileaflet bovine pericardial tissue valve, a polyethylene terephthalate (PET) internal fabric skirt, and a PET external sealing skirt for reduction of paravalvular regurgitation. The leaflets are treated according to the Carpentier Edwards ThermaFix process.

**Figure 1: SAPIEN 3 Transcatheter Heart Valve**

The SAPIEN 3 Ultra THV (model 9750TFX, 20, 23, and 26 mm), as shown in Figure 2, is a design iteration of the SAPIEN 3 THV, with a knitted outer skirt featuring a velour texture on one side.

**Figure 2: SAPIEN 3 Ultra Transcatheter Heart Valve**
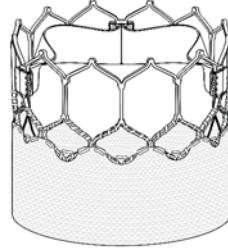
The Edwards Commander Delivery System (models 9600LDS20, 9600LDS23, 9600LDS26, and 9600LDS29), as shown in Figure 3, includes a handle that provides a flex wheel for articulation of the flex catheter, a tapered tip at the distal end of the delivery system, a balloon catheter for deployment of the THV, and radiopaque markers. It is used when a long access route is planned.

Figure 3: Edwards Commander Delivery System
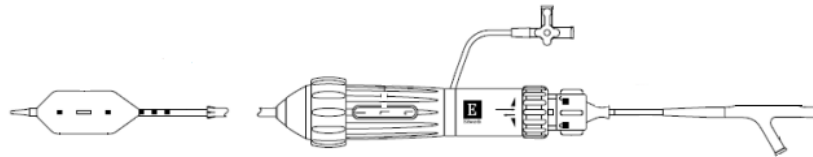
The Edwards SAPIEN 3 Ultra Delivery System (models 9630TF20, 9630TF23, 9630TF26, and 9630TF29), as shown in Figure 4, includes a handle that provides a flex wheel to control flexing of the flex catheter, a fine adjustment wheel to facilitate THV positioning, a tapered tip at the distal end, and a radiopaque positioning marker in the balloon. It is also used when a long access route is planned.

**Figure 4: Edwards SAPIEN 3 Ultra Delivery System**
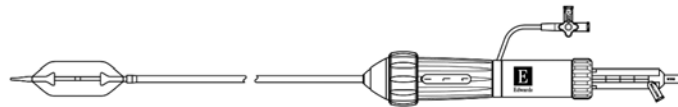
The Edwards Certitude Delivery System (models 9630TA20, 9600SDS20, 9630TA23, 9600SDS23, 9630TA26, 9600SDS26, 9630TA29, and 9600SDS29), as shown in Figure 5, includes a handle with a flex wheel for articulation of the balloon catheter and extension tubing. It is used when a short access route is planned.

Figure 5: Edwards Certitude Delivery System

The Edwards eSheath Introducer Set (models 914ES and 916ES), as shown in Figure 6, consists of a hydrophilic coated, expandable sheath and 2 dilators. It is available in 14 and 16 Fr inner diameters.

Figure 6: Edwards eSheath Introducer Set
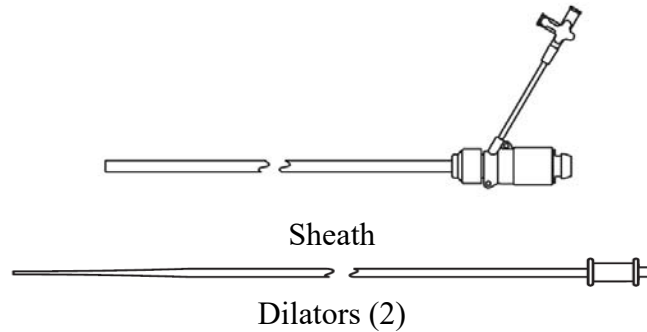
Sheath

Dilators (2)

The Edwards Axela Sheath (model 9630ES14), as shown in Figure 7, also consists of a hydrophilic coated, expandable sheath and 2 dilators. It is available in 14 Fr inner diameter.

Figure 7: Edwards Axela Sheath

Sheath

Dilators (2)
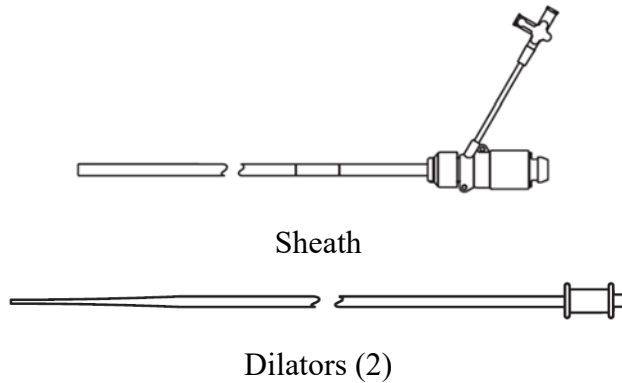
The Edwards Certitude Introducer Sheath (models 9600IS18 and 9600IS21), as shown in Figure 8, has a radiopaque marker for visualization of the sheath tip and non-radiopaque depth markings on the distal end. The proximal end of the introducer sheath includes a flush tube and three hemostasis valves.

Figure 8: Edwards Certitude Introducer Sheath
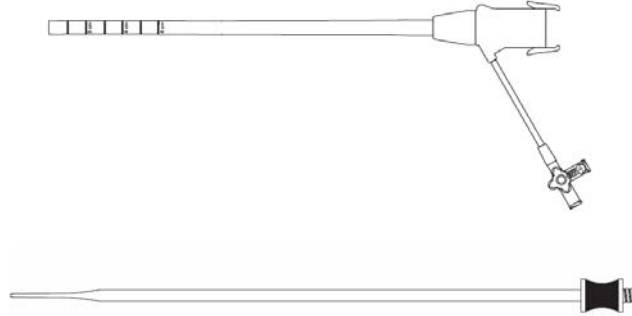
The Qualcrimp crimping accessory, as shown in Figure 9, is a non-patient contacting device that is placed around the THV to protect the leaflets during the crimping process. It is manufactured of tubular polyester polyurethane foam and laminated cylindrically on both the inner and outer surfaces with a polyether urethane material.

Figure 9: Qualcrimp Crimping Accessory

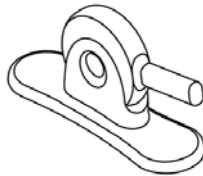The Edwards Crimper (model 9600CR), as shown in Figure 10, is comprised of various molded plastic components which compress the valve to a controlled aperture. The aperture is created by rotating the handle until it abuts the crimp stopper. The Edwards Crimper is used with a Crimp Stopper to correctly crimp the THV.

Figure 10: Edwards Crimper

VI.   ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of severe native calcific aortic stenosis in patients deemed to be at low risk for open surgical therapy, including surgical aortic valve replacement (SAVR), temporary relief using balloon aortic valvuloplasty (BAV), or medical therapy (no obstruction-relieving intervention). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets his/her expectations and lifestyle.

VII. MARKETING HISTORY

The Edwards SAPIEN 3 THV System and Edwards SAPIEN 3 Ultra THV System have not been marketed in the United States or any foreign country for the "low risk" transcatheter aortic valve replacement (TAVR) indication.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

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

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

IX.   SUMMARY OF PRECLINICAL STUDIES

A summary of previously reported preclinical studies can be found in the SSED for the original PMA. No additional preclinical study was performed for the current application.

X.   SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of 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 low risk for open surgical therapy under IDE G150278 (entitled the "PARTNER 3" trial). The data from this study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

The Edwards SAPIEN 3 Ultra THV System was not used in the trial. However, the results obtained on the Edwards SAPIEN 3 THV System are considered applicable to the Edwards

SAPIEN 3 Ultra THV System based on prior demonstration of device comparability in application P140031/S074.

A. Study Design

Patients were enrolled between March 2016 and June 2018. The database for this Panel Track PMA Supplement reflected data collected through December 21, 2018 and included 1000 patients. There were 71 investigational sites in the U.S, Australia, Canada, New Zealand, and Japan.

The PARTNER 3 trial was a prospective, randomized (1:1), controlled, multicenter study to compare TAVR with the Edwards SAPIEN 3 THV to SAVR. A subset of patients were enrolled in a computed tomography (CT) substudy to investigate the prevalence of Hypoattenuated Leaflet Thickening (HALT) and reduced leaflet mobility.

The PARTNER 3 trial 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 Valve Academic Research Consortium-2 (VARC-2) definitions.[1] A CT core laboratory was used for assessment of baseline CTs for annulus dimensions and the CT images acquired in the CT substudy.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the PARTNER 3 trial was limited to patients who met the following inclusion criteria:

   – Severe, calcific aortic stenosis meeting the following criteria:
      o Aortic valve area (AVA) ≤ 1.0 cm^2 or AVA index ≤ 0.6 cm^2/m^2;
      o Jet velocity ≥ 4.0 m/s or mean gradient ≥ 40 mmHg; AND
      o New York Heart Association (NYHA) Functional Class ≥ 2; OR Exercise tolerance test that demonstrates a limited exercise capacity, abnormal BP response, or arrhythmia; OR Asymptomatic with LVEF <50%.
      Note: Qualifying echocardiography must be within the 90 days prior to randomization.
   – Heart team agrees the patient has a low risk of operative mortality and an STS score < 4%.
   – The study patient has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB)/Ethics Committee (EC) of the respective clinical site.

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

   – Native aortic annulus size unsuitable for sizes 20, 23, 26, or 29 mm THV based on 3D imaging analysis

- Iliofemoral vessel characteristics that would preclude safe passage of the introducer sheath
- Evidence of an acute myocardial infarction ≤ 1 month (30 days) before randomization
- Aortic valve is unicuspid, bicuspid, or non-calcified
- Severe aortic regurgitation (>3+)
- Severe mitral regurgitation (>3+) ≥ moderate stenosis
- Pre-existing mechanical or bioprosthetic valve in any position. (of note, mitral ring is not an exclusion)
- Complex coronary artery disease:
    - Unprotected left main coronary artery
    - Syntax score > 32 (in the absence of prior revascularization)
    - Heart Team assessment that optimal revascularization cannot be performed
- Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of randomization
- Leukopenia (WBC < 3000 cell/mL), anemia (Hgb < 9 g/dL), Thrombocytopenia (Plt < 50,000 cell/mL), history of bleeding diathesis or coagulopathy, or hypercoagulable states
- Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of randomization
- Hypertrophic cardiomyopathy with obstruction (HOCM)
- Ventricular dysfunction with left ventricular ejection fraction (LVEF) < 30%
- Cardiac imaging (echocardiography, CT, and/or magnetic resonance imaging) evidence of intracardiac mass, thrombus or vegetation
- Inability to tolerate or condition precluding treatment with anti-thrombotic/anticoagulation therapy during or after the valve implant procedure
- Stroke or transient ischemic attack (TIA) within 90 days of randomization
- Renal insufficiency (eGFR < 30 ml/min per the Cockcroft-Gault formula) and/or renal replacement therapy at the time of screening.
- Active bacterial endocarditis within 180 days of randomization
- Severe lung disease (FEV1 < 50% predicted) or currently on home oxygen
- Severe pulmonary hypertension (e.g., pulmonary artery systolic pressure ≥ 2/3 systemic pressure)
- History of cirrhosis or any active liver disease
- Significant frailty as determined by the Heart Team (after objective assessment of frailty parameters).
- Significant abdominal or thoracic aortic disease (such as porcelain aorta, aneurysm, severe calcification, aortic coarctation, etc.) that would preclude safe passage of the delivery system or cannulation and aortotomy for SAVR
- Hostile chest or conditions or complications from prior surgery that would preclude safe reoperation (i.e., mediastinitis, radiation damage, abnormal chest wall, adhesion of aorta or internal mammary artery to sternum, etc.)
- Patient refuses blood products
- Body mass index (BMI) > 50 kg/m^2
- Estimated life expectancy < 24 months

- Absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with pre-medication
- Immobility that would prevent completion of study procedures (e.g. six-minute walk tests, etc.)
- Patient is not a candidate for both arms of the study (not applicable to single-arm registries)
- Currently participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials. Observational studies are not considered exclusionary.

Patients were excluded from the CT substudy if the following was present:
- Condition requiring or planned use of anticoagulants following the valve implant procedure
- GFR < 50
- Inability to perform high-quality multiple detector CT study for any reason (e.g., atrial fibrillation with rapid ventricular response).

2. Follow-up Schedule

Follow-up periods were discharge, 30 days, 6 months, and 1 year, and will continue annually thereafter to 10 years post procedure. Preoperative and post-operative assessments included physical assessment and patient interview, laboratory measurements, imaging tests, and quality of life (QoL) questionnaires. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

The primary endpoint was a composite of all-cause mortality, all stroke, and rehospitalization (valve-related or procedure-related and including heart failure) at 1 year post procedure. The endpoint was evaluated as a non-inferiority analysis of the risk difference based on a non-inferiority margin of 6.0%. The primary hypothesis was as follows:

$$H_0: r_T - r_C \geq \triangle$$
$$H_A: r_T - r_C < \triangle$$

where r_T and r_C denote the event proportions in the test arm and control arm, respectively, and $\triangle$ denotes the non-inferiority margin. The $\triangle$ value was chosen to be 6.0%. The test was performed at a one-sided α level of 0.025. The 95% confidence interval for the difference $r_T - r_C$ was computed using the Kaplan-Meier algorithm with the standard errors being computed using the Greenwood's formula. The null hypothesis was rejected at $\alpha = 0.025$ if the upper 95% confidence limit was less than 6.0%.

Once non-inferiority was demonstrated for the primary endpoint, testing for superiority of TAVR with SAPIEN 3 as compared to SAVR was performed sequentially on six select

secondary endpoints, including the primary endpoint and five (5) additional secondary endpoints, as shown in the order below:

    (1) New onset atrial fibrillation at 30 days
    (2) Length of index hospitalization
    (3) Composite of all-cause mortality, all stroke, and rehospitalization at 1 year
    (4) Death, Kansas City Cardiomyopathy Questionnaire (KCCQ) < 45 or KCCQ
        decrease $\geq$ 10 points at 30 days
    (5) Composite of death and all stroke at 30 days
    (6) All stroke at 30 days

The hypothesis for each of the above superiority endpoints was as follows:

$$H_0: r_T = r_C$$
$$H_A: r_T \neq r_C$$

For endpoints (1) and (4)-(6) above, the trial arms were compared using the Fisher's exact test; for endpoint (2) above, the trial arms were compared using the Wilcoxon rank-sum test; and for endpoint (3) above, the trial arms were compared using the same statistics as the non-inferiority assessment. All tests were performed at a one-sided α level of 0.025. To keep the overall type I error of 0.05, a gatekeeping method was applied for multiplicity adjustment.[2, 3]

B. Accountability of the PMA Cohort

At the time of database lock, a total of 1000 patients were randomized in the study, including 503 TAVR patients and 497 SAVR patients.

There were three different analysis populations defined in the protocol: Intention-to-Treat (ITT), As Treated (AT), and Valve Implant (VI), as summarized in Table 1 and Figure 11. The primary analysis was the AT analysis.

Table 1: Analysis Populations

Analysis Population	Definition	Number of Patients	
		TAVR	**SAVR**
Intention-To-Treat (ITT)	All randomized patients.	503	497
As Treated (AT)	All ITT patients for whom the index procedure was begun, whether or not the index procedure was completed.	496	454
Valve Implant (VI)	All AT patients who received and retained the intended valve during the index procedure.	495	453

Figure 11: Patient Population Flowchart
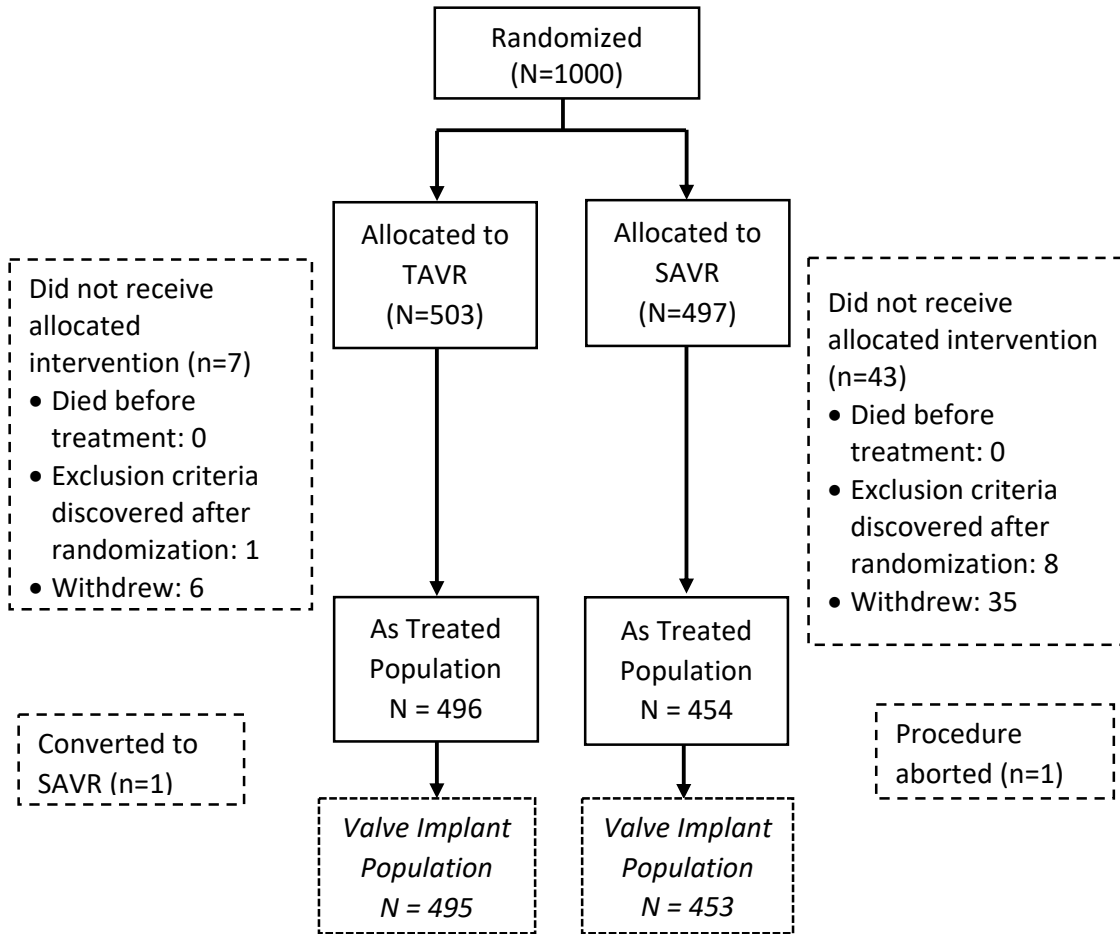
The overall follow-up compliance of the trial is summarized in Table 2.

Table 2: Overall Study Compliance (AT Population)

Patient Accountability	30-day Visit		1 Year Visit	
	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)
Total patients	496	454	496	454
Non-eligible	2	11	6	30
Death	2	6	5	11
Withdrawal	0	3	0	12
Lost to follow-up	0	0	0	1
Exit with other reason	0	2	1	6

Patient Accountability	30-day Visit		1 Year Visit	
	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)
Visit not yet due	0	0	0	0
Eligible	494	443	490	424
Follow-up visit completed	96.5% (493)	96.5% (438)	97.8% (485)	91.2% (414)
Missed visit	0.2% (1)	1.1% (5)	1.0% (5)	2.2% (10)

C. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population are typical for a TAVR study performed in the U.S., as shown in Table 3. The treatment cohorts were generally well balanced with respect to age, gender, and STS risk score.

Table 3: Patient Demographics and Baseline Characteristics (AT Population)

Demographics and Baseline Characteristics	Summary Statistics*	
	TAVR (N = 496)	SAVR (N = 454)
Age - years	73.3 ± 5.8	73.6 ± 6.1
Male sex	67.5% (335/496)	71.1% (323/454)
Society of Thoracic Surgeons (STS) score, %	1.9 ± 0.7	1.9 ± 0.6
New York Heart Association (NYHA) class		
I/II	68.8% (341/496)	76.2% (346/454)
III/IV	31.1% (155/496)	23.8% (108/454)
Previous myocardial infarction	5.7% (28/495)	5.8% (26/452)
Previous intervention		
Coronary artery bypass grafting (CABG)	3.0% (15/494)	1.8% (8/451)
Percutaneous coronary intervention (PCI)	18.8% (93/494)	16.2% (73/452)
Stroke or cerebrovascular accident (CVA)	3.4% (17/496)	5.1% (23/453)
Peripheral vascular disease (PVD)	6.9% (34/494)	7.3% (33/453)
Atrial fibrillation	15.7% (78/496)	18.8% (85/453)
Atrial flutter	3.0% (15/496)	2.4% (11/452)
Permanent pacemaker or defibrillator	2.4% (12/496)	2.9% (13/454)
Hostile chest	0.0% (0/496)	0.0% (0/454)
Echocardiographic findings (Valve Implant Population)		
Valve area (cm^2)	0.8 ± 0.2 (459)	0.8 ± 0.2 (424)

Demographics and Baseline Characteristics	Summary Statistics[*]	
	TAVR (N = 496)	SAVR (N = 454)
Mean gradient (mmHg)	49.4 ± 12.8 (484)	48.3 ± 11.8 (442)
Mean left ventricular ejection fraction (LVEF), %	65.7 ± 9.0 (472)	66.2 ± 8.6 (436)
Moderate or severe aortic regurgitation	3.9% (19/484)	2.5% (11/446)
Moderate or severe mitral regurgitation	1.3% (6/477)	3.2% (14/437)

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

D. Safety and Effectiveness Results

1. Primary Endpoint

The primary endpoint results are presented in Table 4 and Figure 12. The rate of all-cause death, all stroke, or rehospitalization (valve-related or procedure-related and including heart failure) at 1 year was 8.5% in the TAVR cohort and 15.1% in the SAVR cohort. Since the upper limit of the 95% confidence interval for the difference in the primary endpoint event rate was < 6.0%, non–inferiority was achieved.

Table 4: Primary Endpoint Analysis (AT Population)

Event	Kaplan-Meier Rate[*]		Difference of KM Estimate (TAVR – SAVR)	95% CI for the Difference	Non-inferiority Criterion
	TAVR (N=496)	SAVR (N=454)			
All-cause death, all stroke, or rehospitalization	8.5% (42)	15.1% (68)	-6.65%	[-10.77%, -2.52%]	Pass
All-cause death	1.0% (5)	2.5% (11)	-1.44%	[-3.13%, 0.24%]	
All stroke	1.2% (6)	3.1% (14)	-1.90%	[-3.77%, -0.02%]	
Rehospitalization	7.3% (36)	11.0% (49)	-3.74%	[-7.45%, -0.02%]	

[*]Kaplan-Meier estimate - % (no. of patients with the event)

Figure 12: All-Cause Death, All Stroke, and Rehospitalization through 1 Year (AT Population)
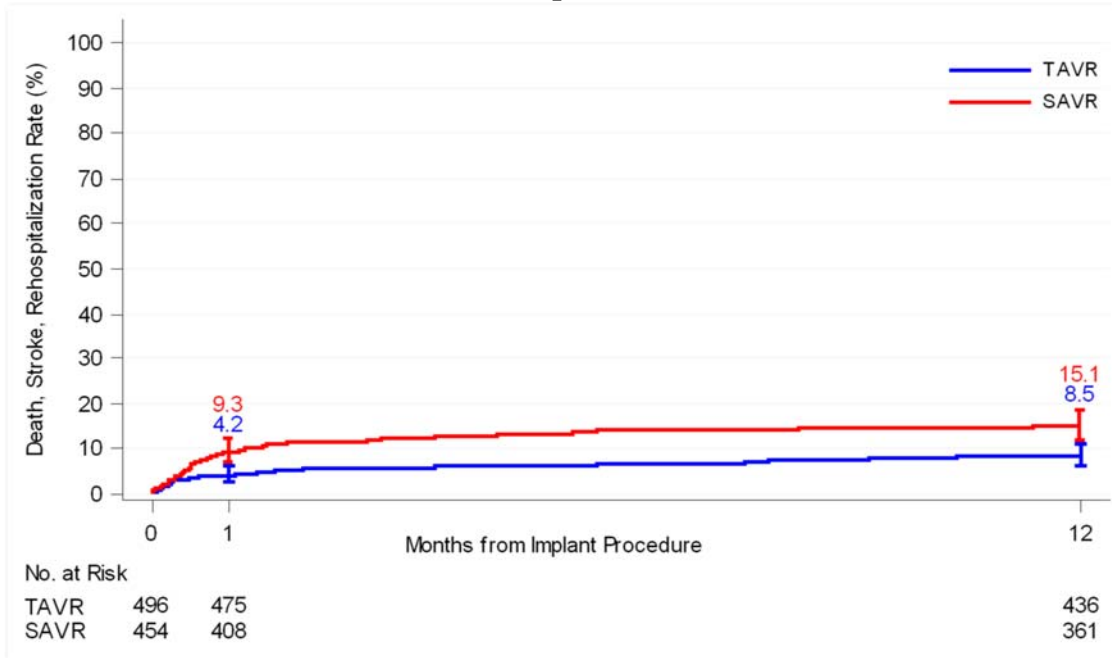
Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

2. Secondary Endpoints

Hypothesis testing

Since the primary endpoint passed the non-inferiority testing, the prespecified superiority testing was carried out on the six select secondary endpoints sequentially. TAVR with SAPIEN 3 was found to be superior to SAVR in all six secondary endpoints, as shown in Table 5.

Table 5: Superiority Testing of Select Secondary Endpoints (AT Population)

No.	Endpoint	Summary Statistics*		Difference (TAVR – SAVR)	95% CI for the Difference	p-value (Superiority Test Result)
		TAVR (N=496)	SAVR (N=454)			
1	New onset atrial fibrillation at 30 days†	5.0% (21/417)	39.3% (145/369)	-34.3%	[-39.7%, -28.9%]	<.0001 (pass)

No.	Endpoint	Summary Statistics*		Difference (TAVR – SAVR)	95% CI for the Difference	p-value (Superiority Test Result)
		TAVR (N=496)	SAVR (N=454)			
2	Length of index hospitalization (days)	2.9 ± 0.1 (496)	7.4 ± 0.2 (454)	-4.5	[-4.8, -4.1]	<.0001 (pass)
3	All-cause death, all stroke, or rehospitalization at 1 year	8.5% (42)	15.1% (68)	-6.6%	[-10.8%, -2.5%]	0.0016 (pass)
4	Death, KCCQ < 45 or KCCQ decrease from baseline ≥ 10 points at 30 days	3.9% (19/492)	30.6% (133/435)	-26.7%	[-31.4%, -22.1%]	<.0001 (pass)
5	Death or all stroke at 30 days	1.0% (5/496)	3.3% (15/454)	-2.3%	[-4.2%, -0.4%]	0.0214 (pass)
6	All stroke at 30 days	0.6% (3/496)	2.4% (11/454)	-1.8%	[-3.4%, -0.2%]	0.0284 (pass)

*Continuous measures - Mean ± SE (Total no.); Categorical measures – observed rate, % (no./Total no.), except No. 3 - Kaplan-Meier rate, % (Total no.).
†Patients with pre-procedural atrial fibrillation were excluded from the analysis.

Valve Performance

The effective orifice area (EOA), mean aortic gradient, total aortic regurgitation (AR), and paravalvular regurgitation values obtained over time for the TAVR and SAVR patients are shown in Figure 13 through Figure 16, respectively. The increase in EOA and decrease in gradient were sustained through 1 year in both cohorts. In the TAVR cohort, the proportion of patients with total AR ≥ moderate was 0.8% at 30 days and 1.1% at 1 year, while in the SAVR cohort, the corresponding proportion was 0.4% at 30 days and 0.6% at 1 year. The proportion of patients with paravalvular regurgitation ≥ moderate was 0.8% at 30 days and 0.6% at 1 year in the TAVR cohort, as compared to 0.0% at 30 days and 0.8% at 1 year in the SAVR cohort.

Figure 13: Effective Orifice Area (VI Population)
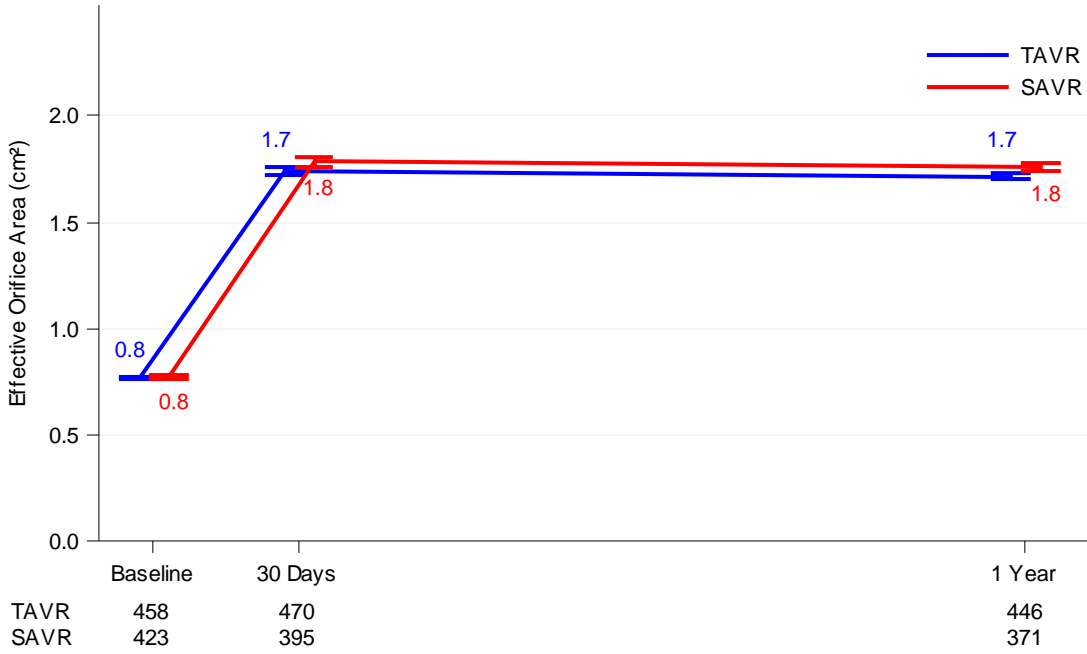
	Baseline	30 Days		1 Year
TAVR	458	470		446
SAVR	423	395		371

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

Figure 14: Mean Aortic Gradient (VI Population)
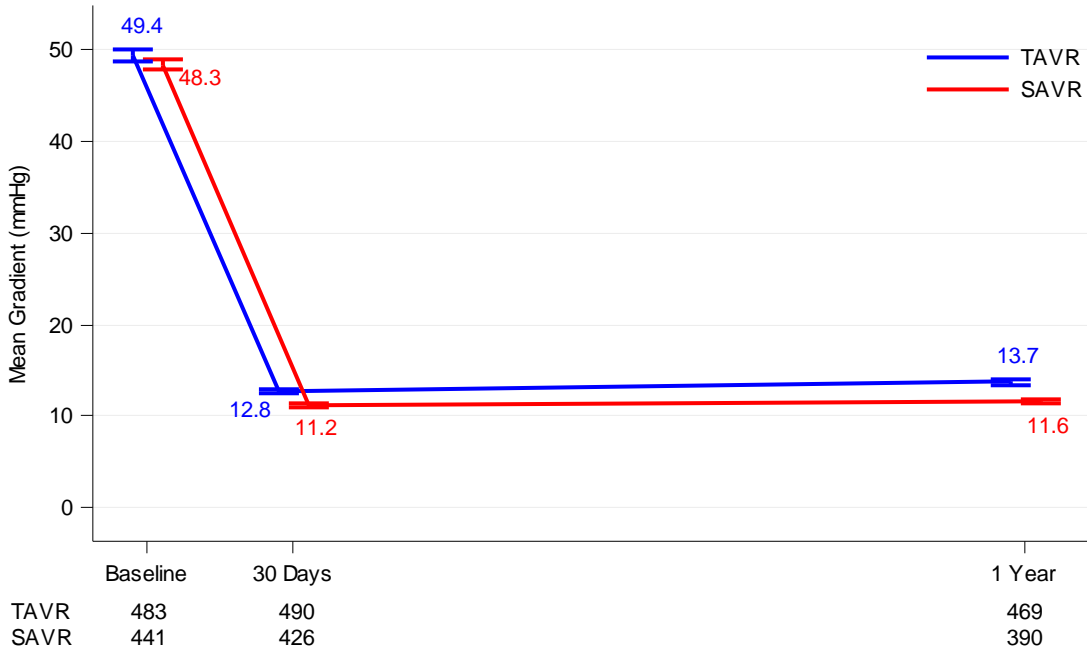
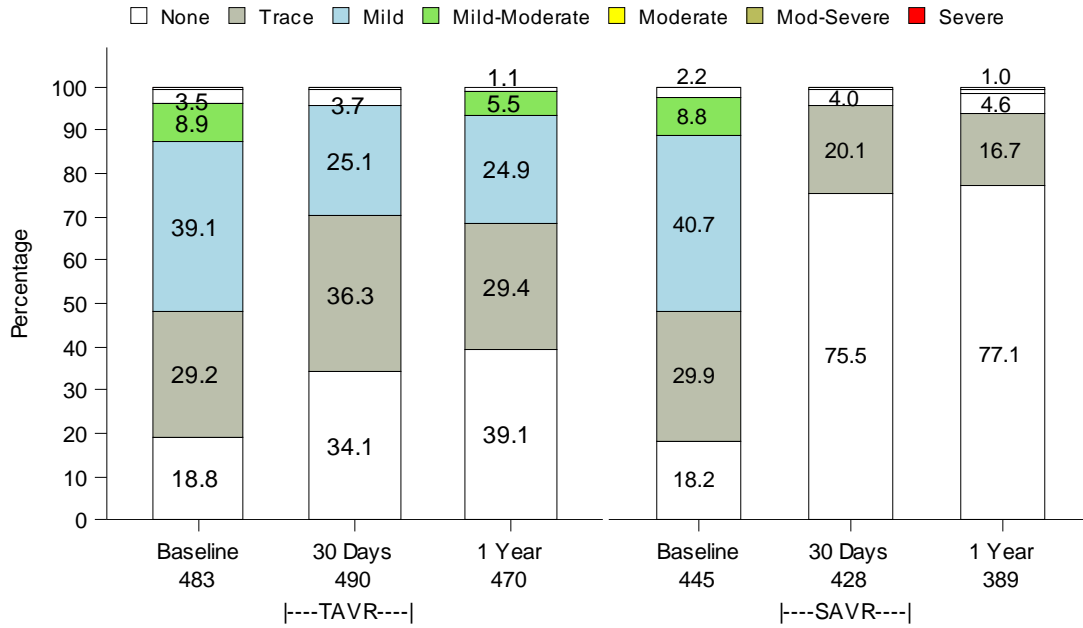|	Baseline	30 Days		1 Year
TAVR	483	490		469
SAVR	441	426		390

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

Figure 15: Total Aortic Regurgitation (VI Population)

Legend: None, Trace, Mild, Mild-Moderate, Moderate, Mod-Severe, Severe

Percentage

TAVR:
- Baseline (483): None 18.8, Trace 29.2, Mild 39.1, Mild-Moderate 8.9, 3.5
- 30 Days (490): None 34.1, Trace 36.3, Mild 25.1, 3.7
- 1 Year (470): None 39.1, Trace 29.4, Mild 24.9, Mild-Moderate 5.5, 1.1

|----TAVR----|

SAVR:
- Baseline (445): None 18.2, Trace 29.9, Mild 40.7, Mild-Moderate 8.8, 2.2
- 30 Days (428): None 75.5, Trace 20.1, 4.0
- 1 Year (389): None 77.1, Trace 16.7, 4.6, 1.0

|----SAVR----|

Figure 16: Paravalvular Regurgitation (VI Population)

Legend: None, Trace, Mild, Mild-Moderate, Moderate, Mod-Severe, Severe

Percentage

TAVR:
- 30 Days (487): None 35.7, Trace 34.7, Mild 25.1, 3.7
- 1 Year (466): None 42.7, Trace 27.3, Mild 24.2, 5.2

|----TAVR----|

SAVR:
- 30 Days (421): None 88.1, Trace 9.0, 2.9
- 1 Year (381): None 90.3, Trace 7.1, 1.8

|----SAVR----|

NYHA Functional Class

The NYHA classifications by visit are presented in Figure 17. At baseline, 31.3% of TAVR patients and 23.6% of SAVR patients were in NYHA III/IV. At 1 year, the majority (~99%) of TAVR and SAVR patients were in NYHA Class I/II.

Figure 17: NYHA Class by Visit (VI Population)

Legend: I (gray), II (green), III (yellow), IV (red)

	TAVR			SAVR		
	Baseline 495	30 Days 492	1 Year 479	Baseline 453	30 Days 433	1 Year 407
IV	0.6	1.2	1.0	1.1	4.4	1.5
III	30.7			22.5		
II	68.3	18.5	16.7	74.8	28.9	15.2
I	0.4	80.3	82.3	1.5	66.7	83.3
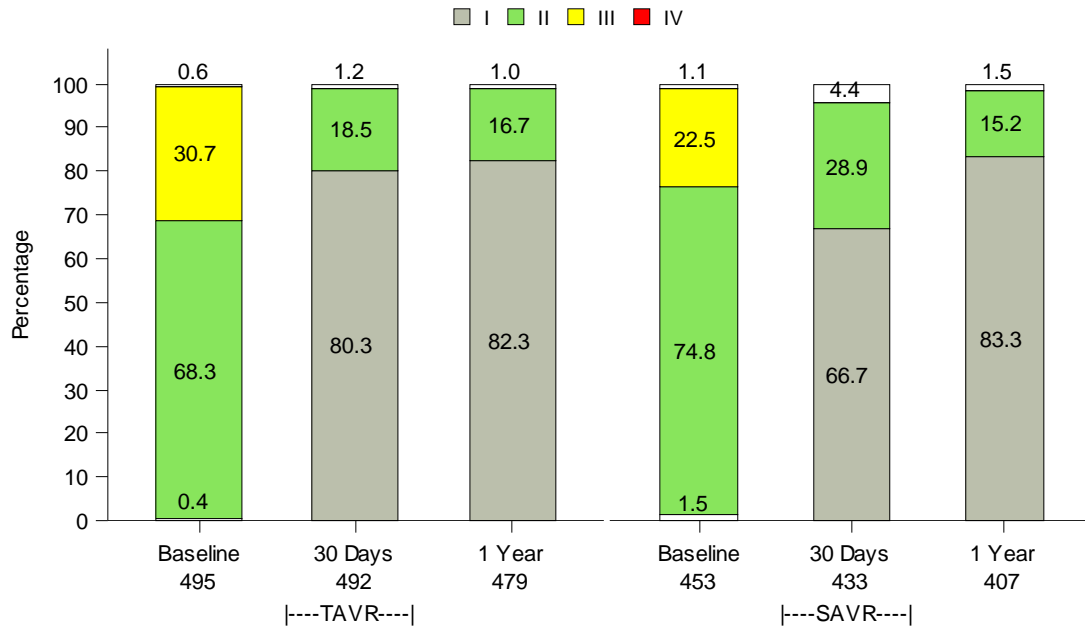
Six-Minute Walk Test (6MWT)

The results for the 6MWT are presented in Figure 18. The TAVR patients showed an increase in mean 6MWT distance from 331.0 m at baseline to 349.1 m at 30 days, while SAVR patients showed a decrease from 329.4 m at baseline to 314.4 m at 30 days. The two cohorts had similar values at 1 year (347.6 m for TAVR and 351.7 m for SAVR).

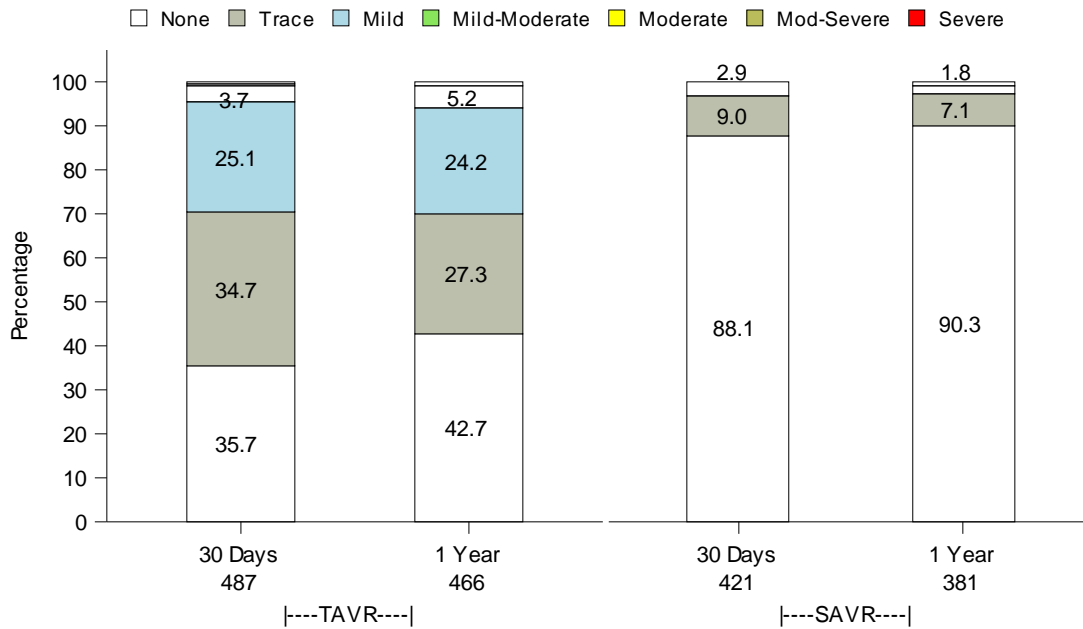**Figure 18: 6MWT Distance (VI Population)**
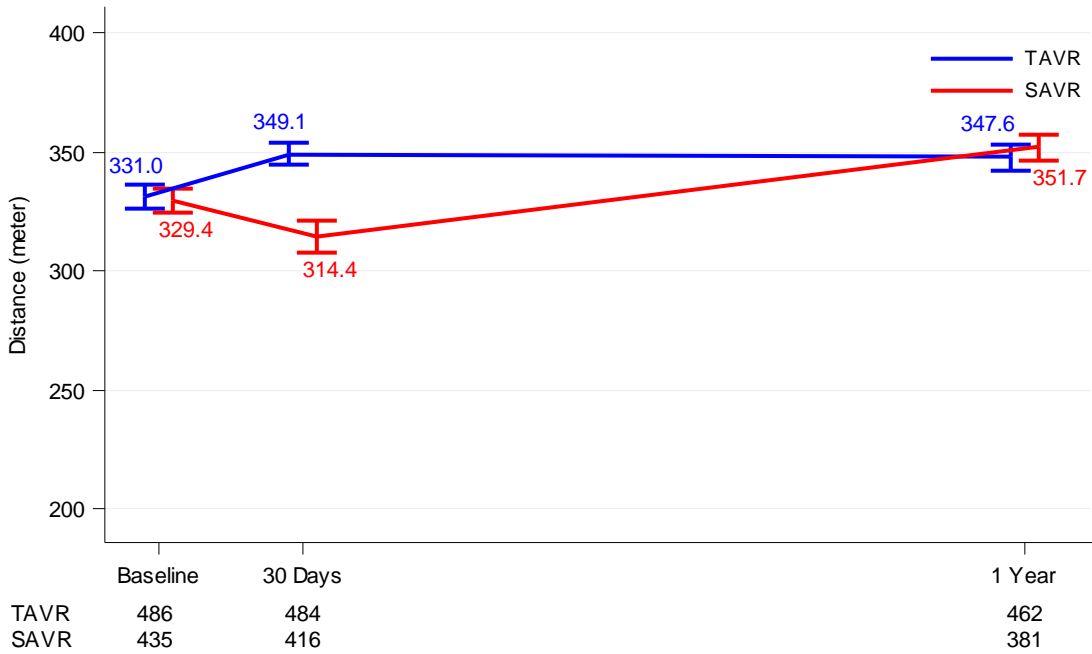
Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

QoL

KCCQ

The results for the KCCQ overall summary score are presented in Figure 19. The mean score increased from 70.3 at baseline to 88.9 at 30 days and 89.9 at 1 year in TAVR patients and from 70.1 at baseline to 72.8 at 30 days and 88.1 at 1 year in SAVR patients.

Figure 19: KCCQ Overall Summary Score (VI Population)

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

EuroQol (EQ-5D)

The results for the EQ-5D visual analog score (VAS) are presented in Figure 20. The mean score was 74.2 at baseline, 85.2 at 30 days, and 84.4 at 1 year in TAVR patients, as compared to 75.2 at baseline, 76.5 at 30 days, and 84.7 at 1 year in SAVR patients.

Figure 20: EQ-5D Visual Analog Score (VI Population)

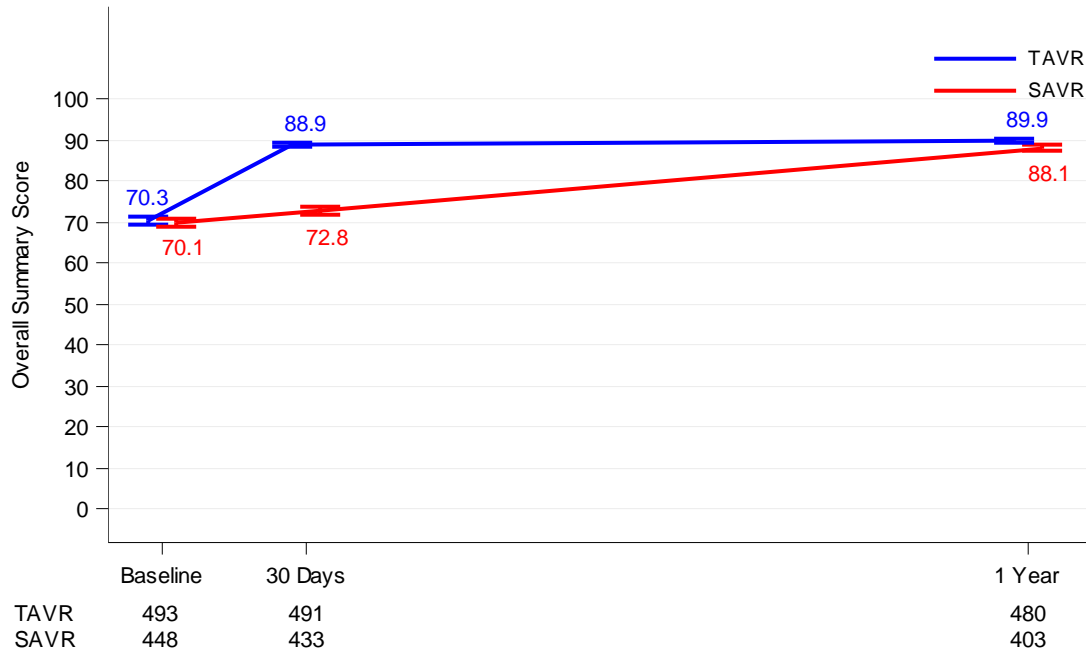|	Baseline	30 Days	1 Year
TAVR	490	490	478
SAVR	442	428	403

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

Short Form (SF)-36

The results for the SF-36 physical component summary score and mental component summary score are presented in Figure 21 and Figure 22, respectively.

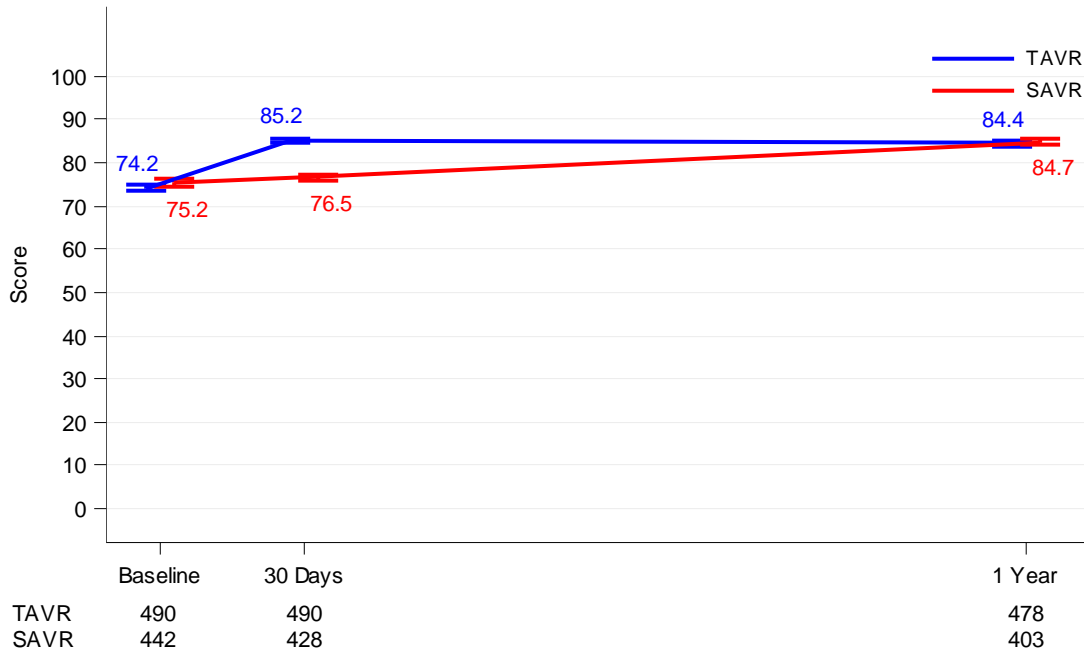**Figure 21: SF-36 Physical Component Summary Score (VI Population)**

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

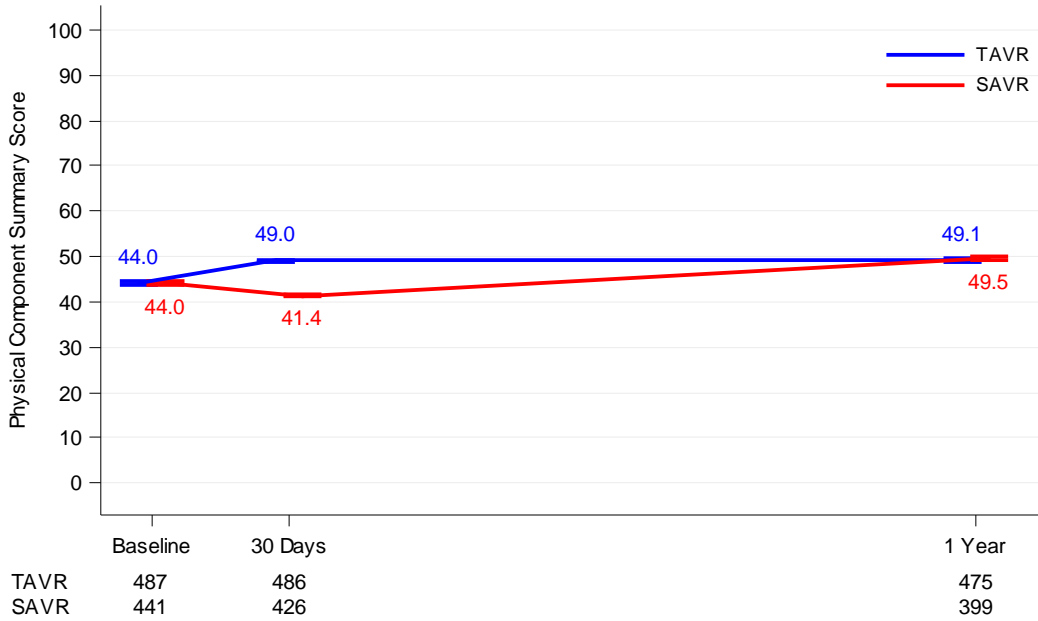**Figure 22: SF-36 Mental Component Summary Score (VI Population)**

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

3. Adverse Events

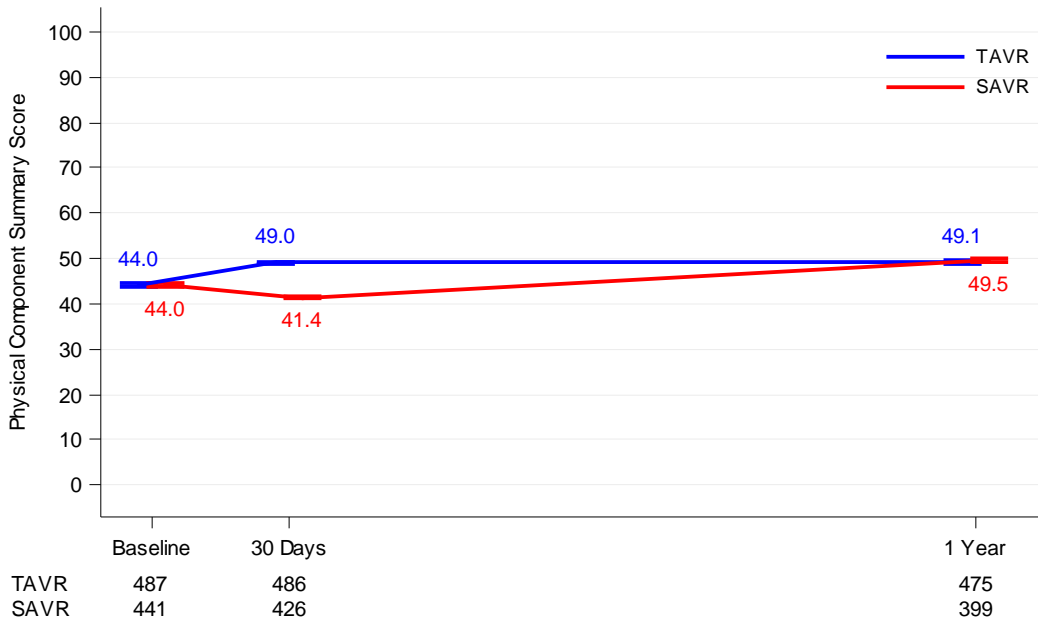The Kaplan-Meier estimates of the CEC-adjudicated adverse events through 1 year are presented in Table 6.

Table 6: CEC-Adjudicated Adverse Events through 1 Year (AT Population)

Event	Kaplan-Meier Rate[*]			
	30 Days		1 Year	
	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)
All cause death	0.4% (2, 2)	1.1% (5, 5)	1.0% (5, 5)	2.5% (11, 11)
Cardiovascular death	0.4% (2, 2)	0.9% (4, 4)	0.8% (4, 4)	2.0% (9, 9)
All stroke	0.6% (3, 3)	2.4% (11, 11)	1.2% (6, 6)	3.1% (14, 14)
Disabling stroke	0.0% (0, 0)	0.4% (2, 2)	0.2% (1, 1)	0.9% (4, 4)
Non-disabling stroke	0.6% (3, 3)	2.0% (9, 9)	1.0% (5, 5)	2.2% (10, 10)
Death or stroke	1.0% (5, 5)	3.3% (16, 15)	1.8% (11, 9)	4.9% (25, 22)
Death or disabling stroke	0.4% (2, 2)	1.3% (7, 6)	1.0% (6, 5)	2.9% (15, 13)
Major vascular complications	2.2% (12, 11)	1.5% (8, 7)	2.8% (15, 14)	1.5% (8, 7)
Life-threatening / disabling, or major bleeding	3.6% (22, 18)	24.5% (123, 111)	7.7% (45, 38)	25.9% (132, 117)
Life-threatening / disabling bleeding	1.2% (9, 6)	11.9% (58, 54)	2.8% (17, 14)	12.8% (63, 58)
Major bleeding	2.6% (13, 13)	13.5% (65, 61)	5.3% (28, 26)	14.2% (69, 64)
Myocardial infarction	1.0% (5, 5)	1.3% (6, 6)	1.2% (6, 6)	2.2% (10, 10)
Requirement for renal replacement[†]	0.2% (1, 1)	0.7% (3, 3)	0.2% (1, 1)	0.7% (3, 3)
New permanent pacemaker implantation resulting from new or worsened conduction disturbances[‡]	6.5% (32, 32)	4.0% (18, 18)	7.3% (36, 36)	5.4% (24, 24)
Coronary obstruction requiring intervention	0.2% (1, 1)	0.7% (3, 3)	0.2% (1, 1)	0.7% (3, 3)
New onset atrial fibrillation	5.0% (21, 21)	39.5% (145, 145)	7.0% (29, 29)	40.9% (150, 150)
Rehospitalization[‖]	3.4% (18, 17)	6.5% (30, 29)	7.3% (39, 36)	11.0% (59, 49)

[*]Kaplan-Meier rate (no. of events, no. of patients with the event).

[†]Requirement for renal replacement was based on the site-reported event. All the other events were based on the CEC-adjudicated results.

[‡]Patients with pacemaker or ICD at baseline were not counted as new events.

[‖]Rehospitalization (valve-related or procedure-related and including heart failure).
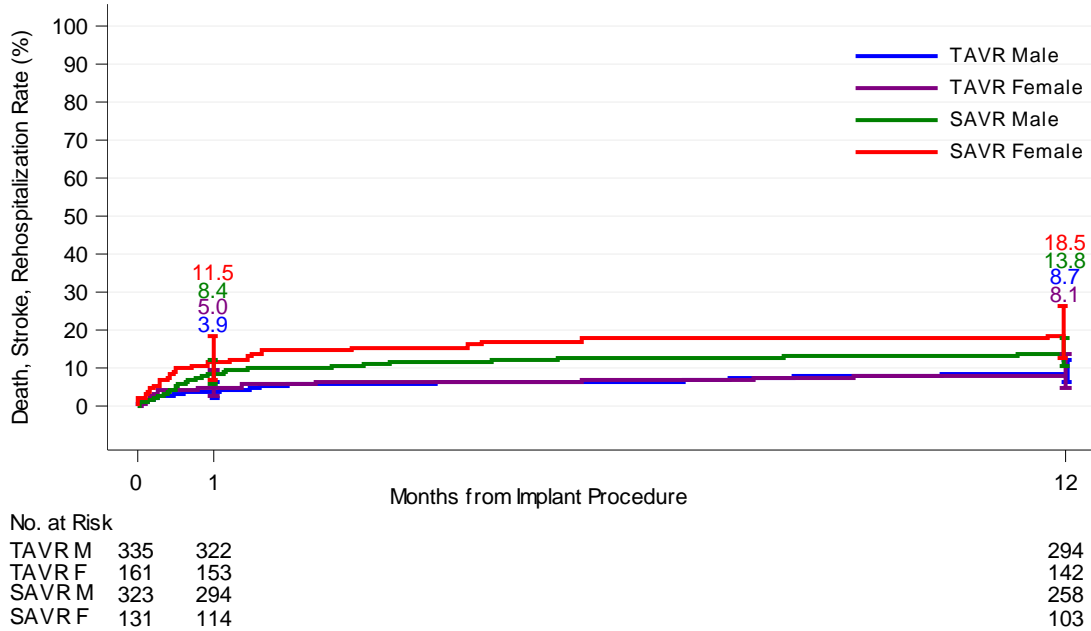
4.   Subgroup Analysis

Gender Analysis

The protocol specified a subgroup analysis on gender. The primary endpoint result stratified by gender is presented in Figure 23.

Figure 23: All-Cause Death, All Stroke, and Rehospitalization through 1 Year Stratified by Gender (AT Population)

No. at Risk					
TAVR M	335	322			294
TAVR F	161	153			142
SAVR M	323	294			258
SAVR F	131	114			103

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.

5.   Other Study Observations

Procedural Information

The general procedural data are summarized in Table 7. Conscious sedation was used in the majority of TAVR patients (65.1%). The mean procedure time was significantly lower for TAVR compared to SAVR (58.6 minutes vs. 208.3 minutes). There were less concomitant (planned) procedures performed for TAVR patients compared to SAVR patients (6.9% vs. 26.4%). Additional TAVR and SAVR specific procedural data are presented in Table 8 and 9, respectively.

Table 7: General Procedural Data (AT Population)

Variable	Summary Statistics[*]	
	TAVR (N=496)	SAVR (N=454)
Subject treated according to their treatment assignment	99.8% (495/496)	99.8% (453/454)
Procedure aborted	0	1
Subject was assigned to TAVR but received SAVR	1	0
Procedure time (min)	58.6 ± 1.6 (496)	208.3 ± 2.9 (454)
Anesthesia type		
General	33.3% (165/496)	100.0% (454/454)
Conscious sedation	65.1% (323/496)	NA
Conversion from conscious sedation to general anesthesia during the procedure	1.6% (8/496)	NA
Anesthesia time (min)	138.7 ± 2.20 (496)	309.7 ± 3.7 (454)
Concomitant procedures	6.9% (34/496)	26.4% (120/454)
Annular area (mm^2)	473.5 ± 83.3 (486)	479.6 ± 87.6 (441)

[*]Continuous measures – mean ± SE (n) for procedure and anesthesia time, mean ± SD (n) for annular area; Categorical measures - % (no./Total no.)

Table 8: TAVR Procedure Data (AT Population)

Variable	Summary Statistics[*]
	TAVR (N=496)
Valve size	
20 mm	2.2% (11/496)
23 mm	29.2% (145/496)
26 mm	47.6% (236/496)
29 mm	21.0% (104/496)
Successful access, delivery and retrieval of the device delivery system	99.8% (494/495)
Arterial access method	
Left percutaneous	22.2% (109/490)
Right percutaneous	76.7% (376/490)
Left surgical cutdown	0.0% (0/490)

Variable	Summary Statistics[*]
	TAVR (N=496)
Right surgical cutdown	1.0% (5/490)
Total fluoroscopy time (min)	13.9 ± 0.3 (487)
BAV performed	57.8% (286/495)
Post dilatation performed	20.9% (103/494)
Number of post dilatations	
1	89.3% (92/103)
2	8.7% (9/103)
3	1.9% (2/103)
More than one SAPIEN 3 THV implanted	0.2% (1/495)

[*]Continuous measures - mean ± SE (n); categorical measures - % (no./Total no.). For patients in whom the procedure was aborted or who were converted to surgery, the rest of the procedure data except valve size were not collected.

Table 9: SAVR Procedure Data (AT Population)

Variable	Summary Statistics[*]
	SAVR (N=454)
Procedure aborted[†]	0.2% (1/454)
Valve size	
19 mm	2.9% (13/453)
21 mm	17.2% (78/453)
23 mm	36.6% (166/453)
25 mm	35.5% (161/453)
27 mm	6.8% (31/453)
29 mm	0.9% (4/453)
Total aortic cross clamp time (min)	74.3 ± 1.3 (453)
Total pump time (min)	97.7 ± 1.6 (453)
SAVR approach	
Sternotomy	95.4% (432/453)
Thoracotomy	0.9% (4/453)
Mini right upper thoracotomy	2.9% (13/453)
Port access	0.2% (1/453)

Variable	Summary Statistics[*]
	SAVR (N=454)
Other	0.7% (3/453)
Successful implantation of the surgical valve	100.0% (453/453)

[*]Continuous measures - mean ± SE (n); categorical measures - % (no./Total no.).
[†]For patients in whom the procedure was aborted, the rest of the procedure data were not collected.

CT Substudy

There were 184 TAVR and 162 SAVR patients at 30 days and 160 and 134 patients at 1 year, respectively, who had at least one adequate CT for leaflet assessments. The HALT and leaflet mobility imaging findings are summarized in Table 10, along with the associated mean aortic pressure gradients. The mean aortic pressure gradients at 1 year stratified by HALT and leaflet mobility at 30 days are summarized in Table 11 and Table 12, respectively. The rate of death, stroke or TIA at 1 year stratified by HALT and leaflet mobility at 30 days are summarized in Table 13 and Table 14, respectively. The CT substudy was not powered to compare the relative incidence or the severity of HALT or reduced leaflet mobility between the TAVR and SAVR cohorts, or to determine whether late clinical outcomes were affected by the presence of HALT or reduced leaflet mobility.

Table 10: HALT and Leaflet Mobility Findings and Associated Mean Gradients

Findings	Summary Statistics[*]			
	30 Days		1 Year	
	TAVR (N=184)	SAVR (N=162)	TAVR (N=160)	SAVR (N=134)
Proportion of patients on oral anticoagulants at time of scan	6.0% (11/184)	21.0% (34/162)	8.1% (13/160)	18/134 (13.4%)
HALT[†]				
No thickening	84.8% (156/184)	95.7% (155/162)	74.4% (119/160)	82.1% (110/134)
Mean gradient (mmHg)	12.5 ± 0.3 (156)	10.8 ± 0.3 (155)	13.7 ± 0.4 (115)	11.7 ± 0.4 (106)
<25% leaflet length thickened	4.9% (9/184)	1.2% (2/162)	11.3% (18/160)	7.5% (10/134)
Mean gradient (mmHg)	11.4 ± 0.9 (9)	16.5 ± NA (1)	12.9 ± 0.7 (18)	9.3 ± 1.8 (8)
25%-50% leaflet length thickened	3.3% (6/184)	1.9% (3/162)	6.3% (10/160)	5.2% (7/134)
Mean gradient (mmHg)	13.7 ± 1.7 (6)	9.4 ± 1.4 (3)	13.2 ± 1.8 (10)	15.1 ± 2.4 (7)

Findings	Summary Statistics[*]			
	30 Days		1 Year	
	TAVR (N=184)	SAVR (N=162)	TAVR (N=160)	SAVR (N=134)
50%-75% leaflet length thickened	6.5% (12/184)	0.6% (1/162)	5.0% (8/160)	3.7% (5/134)
Mean gradient (mmHg)	15.2 ± 1.9 (12)	9.8 ± NA (1)	16.9 ± 3.3 (8)	16.1 ± 4.0 (5)
>75% leaflet length thickened	0.5% (1/184)	0.6% (1/162)	3.1% (5/160)	1.5% (2/134)
Mean gradient (mmHg)	10.2 ± NA (1)	16.8 ± NA (1)	20.2 ± 6.2 (5)	9.0 ± 4.2 (2)
Number of leaflets with HALT	6.7% (37/552)	2.3% (11/486)	12.7% (61/480)	8.2% (33/402)
0 leaflets thickening	156	155	119	110
1 leaflet thickening	21	4	26	15
2 leaflets thickening	5	2	10	9
3 leaflets thickening	2	1	5	0
Leaflet mobility[‡]				
Unrestricted	85.3% (145/170)	96.8% (149/154)	77.6% (118/152)	83.% (108/129)
Mean gradient (mmHg)	12.2 ± 0.3 (145)	10.7 ± 0.3 (148)	13.3 ± 0.4 (114)	12.0 ± 0.5 (105)
Partially restricted, restriction limited to base	5.3% (9/170)	1.3% (2/154)	11.8% (18/152)	8.5% (11/129)
Mean gradient (mmHg)	11.4 ± 0.9 (9)	14.6 ± 1.9 (2)	12.5 ± 0.6 (18)	9.9 ± 1.6 (9)
Partially restricted (<50%)	5.3% (9/170)	1.3% (2/154)	3.9% (6/152)	3.1% (4/129)
Mean gradient (mmHg)	15.5 ± 2.4 (9)	10.3 ± 0.5 (2)	14.0 ± 2.8 (6)	15.6 ± 3.0 (4)
Partially restricted (50%-75%)	3.5% (6/170)	0.0% (0/154)	4.6% (7/152)	3.9% (5/129)
Mean gradient (mmHg)	12.8 ± 1.7 (6)	NA	21.8 ± 3.9 (7)	11.3 ± 3.6 (5)
Largely immobile	0.6% (1/170)	0.6% (1/154)	2.0% (3/152)	0.8% (1/129)
Mean gradient (mmHg)	13.3 ± NA (1)	16.8 ± NA (1)	19.5 ± 8.1 (3)	13.1 ± NA (1)
Number of leaflets partially restricted or largely immobile				
0 leaflet	145	149	118	108
1 leaflet	21	2	22	13
2 leaflets	4	2	8	8
3 leaflets	0	1	4	0

	Summary Statistics*			
Findings	**30 Days**		**1 Year**	
	TAVR (N=184)	**SAVR (N=162)**	**TAVR (N=160)**	**SAVR (N=134)**

*Continuous measures - mean ± SE (n); categorical measures - % (no./Total no.). The analysis population included all the patients enrolled in the CT substudy and had at least one adequate CT for leaflet assessments.

†HALT was defined as: the presence of any hyopattenuated leaflet thickening in any singular leaflet as identified by an independent CT core laboratory. The extent of the hypoattenuated leaflet thickening was graded with regards to the entire leaflet as: None, <25%, 25-50%, 50-75%, or >75%. If more than one leaflet had the appearance of HALT, the thickening measure of the most impacted leaflet was used. Presence of any degree of HALT on any one leaflet rendered a finding.

‡Leaflet mobility was determined by an independent CT core laboratory and included: unrestricted, partially restricted mobility limited to the base of a leaflet, partially restricted mobility involving more than the base of the leaflet but less than 50% of the leaflet, partially restricted mobility involving more than 50% of the leaflet but less than 75% of the leaflet, and/or a largely immobile leaflet. Presence of any degree of restriction or immobility on any one leaflet rendered a finding.

Table 11: Mean Aortic Gradient at 1 Year Stratified by HALT at 30 Days

	Summary Statistics*			
	HALT at 30 Days		**No HALT at 30 Days**	
	TAVR (N=28)	**SAVR (N=7)**	**TAVR (N=156)**	**SAVR (N=155)**
Mean gradient	13.6 ± 1.2 (24)	13.7 ± 2.7 (5)	13.6 ± 0.4 (137)	11.8 ± 0.4 (125)

*Mean ± SE (n). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days.

Table 12: Mean Aortic Gradient at 1 Year Stratified by Leaflet Mobility at 30 Days

	Summary Statistics*			
	Reduced Leaflet Mobility at 30 Days		**Unrestricted at 30 Days**	
	TAVR (N=25)	**SAVR (N=5)**	**TAVR (N=145)**	**SAVR (N=149)**
Mean gradient	13.7 ± 1.28 (23)	14.2 ± 3.48 (4)	13.3 ± 0.4 (124)	11.7 ± 0.4 (119)

*Mean ± SE (n). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days.

Table 13: All-Cause Mortality, All Stroke or TIA at 1 Year Stratified by HALT at 30 Days

1-Year Endpoint	Kaplan-Meier Rate[*]			
	HALT at 30 Days		No HALT at 30 Days	
	TAVR (N=28)	SAVR (N=7)	TAVR (N=156)	SAVR (N=155)
All-cause mortality	0.0% (0)	0.0% (0)	1.3% (2)	1.4% (2)
All stroke	0.0% (0)	0.0% (0)	0.7% (1)	0.0% (0)
TIA	5.6% (1)	0.0% (0)	1.3% (2)	0.0% (0)
All-cause mortality or all stroke or TIA	5.6% (1)	0.0% (0)	3.3% (5)	1.4% (2)

[*]Kaplan-Meier rate (no. of patients with event). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days. The Kaplan-Meier analysis used the CT test date as the start date in determining time to event. Presence of any degree of HALT on any one leaflet rendered a finding and inclusion in the HALT cohort.

Table 14: All-Cause Mortality, All Stroke or TIA at 1 Year Stratified by Leaflet Mobility at 30 Days

1-Year Endpoint	Kaplan-Meier Rate[*]			
	Reduced Leaflet Mobility at 30 Days		Unrestricted at 30 Days	
	TAVR (N=25)	SAVR (N=5)	TAVR (N=145)	SAVR (N=149)
All-cause mortality	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
All stroke	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
TIA	6.3% (1)	0.0% (0)	6.3% (1)	0.0% (0)
All-cause mortality or all stroke or TIA	6.3% (1)	0.0% (0)	3.6% (5)	1.4% (2)

[*]Kaplan-Meier rate (no. of patients with event). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days. The Kaplan-Meier analysis used the CT test date as the start date in determining time to event. Reduced leaflet mobility included any of the following assessments: partially restricted limited to base, partially restricted involving more than the base but less than 50% of the leaflet, partially restricted involving more than 50% but less than 75% of the leaflet, and/or largely immobile. Presence of any degree of restriction or immobility on any one leaflet rendered a finding and inclusion in the reduced leaflet mobility cohort.

6. Pediatric Extrapolation

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

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 PARTNER 3 trial involved 588 investigators of which none were full-time or part-time employees of the sponsor and 30 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: 29
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: 1

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 System Devices panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the clinical study, patients overall demonstrated clinically significant improvement in valve hemodynamics from baseline to 1 year. On average, the EOA increased from 0.8 cm^2 at baseline to 1.7 cm^2 at 1 year, and the mean pressure gradient decreased from 49.4 mmHg at baseline to 13.7 mmHg at 1 year in the TAVR patients. These trends were consistent with those observed in the SAVR patients. In the TAVR cohort, the proportion of patients with total AR ≥ moderate was 1.1% at 1 year, while in the SAVR cohort, the proportion was 0.6% at 1 year. The proportion of patients with paravalvular AR ≥ moderate was 0.6% at 1 year, as compared to 0.8% at 1 year in the SAVR cohort.

The improvement in valve hemodynamics in the TAVR patients was further demonstrated through improvements in NYHA classification, 6MWT distance, and QoL. In the TAVR cohort, about 1% of the patients were in NYHA Class III or IV at 1 year as compared to 31.3% at baseline; similar results were seen in the SAVR cohort. The mean 6MWT distance increased from 331.0 m at baseline to 349.1 m at 30 days in the TAVR patients; this

improvement was sustained at 1 year. Similarly, clinically significant improvement in the KCCQ score was observed in the TAVR patients, which increased from 70.3 at baseline to 88.9 and 89.9 at 30 days and 1 year, respectively. In contrast, early improvements in 6MWT distance and KCCQ score at 30 days were not seen with SAVR, although the improvements at 1 year were similar to those seen with TAVR. Furthermore, the mean procedure time and index procedure hospital stay were 58.6 minutes and 2.9 days, respectively, for TAVR, and were significantly shorter compared to SAVR (208.3 minutes and 7.4 days, respectively).

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 Kaplan-Meier estimate of the event rate of all-cause mortality, all stroke, or rehospitalization (valve-related or procedure-related and including heart failure) at 1 year (i.e., the primary endpoint) was 8.5% in the TAVR cohort and 15.1% in the SAVR cohort. TAVR with the SAPIEN 3 device was found to be non-inferior to SAVR in the primary endpoint within a non-inferiority margin of 6%. Subsequent prespecified superiority testing found that TAVR with the SAPIEN 3 device was superior to SAVR in the primary endpoint. The differences in the 1-year rates of all-cause mortality, all stroke, and rehospitalization between TAVR and SAVR patients were -1.44%, -1.90%, -3.74%, respectively. In addition, TAVR patients had significantly lower rate of new onset atrial fibrillation at 30 days than SAVR patients (5.0% vs. 39.3%).

The CT substudy revealed that 15.2% and 25.6% of TAVR patients had various degrees of leaflet thickening at 30 days and 1 year, respectively, as compared to 4.3% and 17.9% of SAVR patients. In addition, various degrees of restricted leaflet mobility were observed in 14.7% of patients at 30 days and 22.4% of patients at 1 year in the TAVR cohort, which was 3.2% and 16.3%, respectively, in the SAVR cohort. The long-term clinical sequelae of these imaging findings are presently unknown.

C. Benefit-Risk Determination

The probable benefits of TAVR with the SAPIEN 3 THV include improved valve hemodynamic performance, improved functional status as measured by the NYHA classification and 6MWT distance, and improved QoL at 1 year post-procedure.

The probable risks of TAVR with the SAPIEN 3 THV include procedure-related complications such as death, stroke, myocardial infarction, major vascular complications, bleeding, conduction disturbance, and requirement for renal replacement.

1. Patient Perspectives

   This application did not include specific information on patient perspectives for TAVR with the SAPIEN 3 THV. However, since TAVR with the SAPIEN 3 THV provides a less invasive alternative to SAVR, FDA believes that many patients would prefer the TAVR therapy. However, the long-term durability of SAPEIN THV compared to surgically implanted valves has not been established. Patients, especially younger ones, should discuss available treatment options with their heart care team to select the appropriate therapy.

In conclusion, given the available information above, the data support that for patients with severe native aortic stenosis who are at low risk for open aortic valve replacement surgery, the probable benefits of TAVR with the SAPIEN 3 THV outweigh the probable risks.

D. **Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of the SAPIEN 3 THV System for the replacement of native aortic valves in symptomatic severe aortic stenosis patients who are deemed to be at low surgical risk. FDA has determined this conclusion is also applicable to the SAPIEN 3 Ultra THV System.

XIII. **CDRH DECISION**

CDRH issued an approval order on August 16, 2019. 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. **Post-Approval Study - Continued Follow-up of the SAPIEN 3 Transcatheter Heart Valve System "Low Risk" Indication Premarket Cohort**: The study will consist of all living patients who were enrolled under the IDE. The objective of this study is to characterize the clinical outcomes annually through 10 years post-procedure. The safety and effectiveness endpoints include all-cause mortality, all stroke (disabling and non-disabling), life-threatening bleeding, requirement for renal replacement, coronary artery obstruction requiring intervention, major vascular complication, valve-related dysfunction requiring repeat procedure, new permanent pacemaker implantation, prosthetic valve endocarditis, prosthetic valve thrombosis, NYHA classification, 6MWT distance, KCCQ score, and hemodynamic performance metrics by Doppler echocardiography.

2. **Edwards SAPIEN 3 Transcatheter Heart Valve System Registry-Based Continued Access Protocol (CAP) Cohort and "Low Risk" Indication Real-World Use Surveillance**: The applicant has agreed to work with the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (TVT) Registry to ensure that FDA surveillance occurs for the registry-based CAP cohort per approved

protocol and for commercial uses of the SAPIEN 3 THV System and SAPIEN 3 Ultra THV System for the "low risk" indication. The surveillances will be carried out to characterize the clinical outcomes of the CAP cohort annually through 10 years post implantation and to assess the real-world use of the commercial SAPIEN 3 THV System and SAPIEN 3 Ultra THV System to ensure that the device is used in appropriate circumstances, respectively. The surveillance of the CAP cohort will consist of all living CAP patients who were enrolled at participating institutions, and the surveillance of the real-world use will involve all consecutive patients treated within the first 2 years that are entered into the TVT Registry (enrollment period). The applicant has also agreed to link the data to the Centers for Medicare and Medicaid Services (CMS) claims database for long-term surveillance of these patients through 10 years post implantation (follow-up duration). This surveillance will monitor the following: (1) device success (intra-procedure); (2) all-cause mortality, all stroke, life-threatening/major bleeding, new requirement for dialysis, peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months; (3) neurological (non-stroke), vascular complications, and quality of life (KCCQ) outcomes at 30 days and 12 months; and (4) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 2-10 year post implantation.

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

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. Food and Drug Administration. FDA Guidance: Multiple Endpoints in Clinical Trials Guidance for Industry (January 2017). Retrieved from https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf
3. Westfall, K. Optimally weighted, fixed sequence, and gatekeeping multiple testing procedures. J Stat Plan Inference 2001; 99:25-40.