

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Aortic valve, prosthesis, percutaneously delivered
Device Trade Name:	Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA 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/S182
Date of FDA Notice of Approval:	April 30, 2025

The original PMA of the Edwards SAPIEN 3 Transcatheter Heart Valve (THV) system, P140031, was first approved on June 17, 2015, with an indication for the treatment of symptomatic severe native calcific aortic stenosis in patients who are judged by a heart team to be at high or greater risk for surgical aortic valve replacement (SAVR). Subsequently, the device was iterated and the indication was expanded via PMA supplements, as summarized below:

- P140031/S010: Approved on August 18, 2016, for the SAPIEN 3 THV system to include patients with symptomatic severe native calcific aortic stenosis who are deemed to be at intermediate risk for SAVR.
- P140031/S028: Approved on June 5, 2017, for the SAPIEN 3 THV system to include patients with a failing (stenosed, insufficient, or combined) surgical bioprosthetic aortic or mitral valve who are deemed to be at high or greater risk for redo SAVR.
- P140021/S085: Approved on August 16, 2019, for the SAPIEN 3 and SAPIEN 3 Ultra THV system to include patients deemed to be at low risk for SAVR.
- P140031/S112: Approved on September 9, 2020, for the SAPIEN 3 and SAPIEN 3 Ultra THV system to include patients with a failing (stenosed, insufficient, or combined) transcatheter bioprosthetic aortic valve who are deemed to be at high or greater risk for redo SAVR.
- P140031/S125: Approved on May 13, 2021, for the SAPIEN 3 and SAPIEN 3 Ultra THV system to include patients with a failing native mitral valve with an annuloplasty ring (i.e., THV-in-Ring) who are deemed to be at high or greater risk for

SAVR.

- P140031/S162: Approved on May 23, 2024, for the SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA THV system to include patients with a failing (stenosed, insufficient, or combined) surgical bioprosthetic mitral valve who are deemed to be at intermediate risk for redo SAVR.

The SSEDs to support the above indications 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
- https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S085B.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S112B.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S125B.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S162B.pdf

The current supplement was submitted to expand the indications for use of the Edwards SAPIEN 3, SAPIEN 3 Ultra and SAPIEN 3 Ultra RESILIA THV system to include patients with asymptomatic severe native calcific aortic stenosis.

II. INDICATIONS FOR USE

The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve system is indicated to reduce the risks associated with progression from asymptomatic to symptomatic severe native calcific aortic stenosis in patients who are judged by a heart team to be appropriate for transcatheter heart valve replacement therapy.

III. CONTRAINDICATIONS

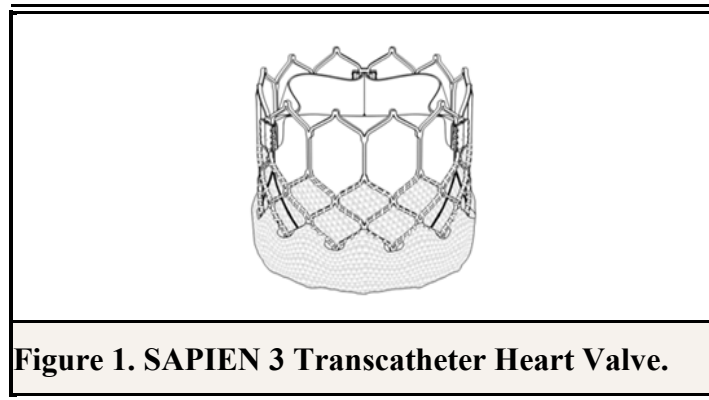
The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA THV system are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

IV. WARNINGS AND PRECAUTIONS

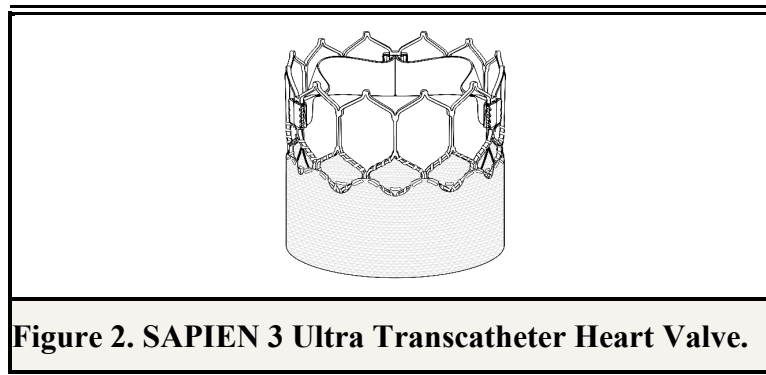
The warnings and precautions can be found in the Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA THV system labeling.

V. DEVICE DESCRIPTION

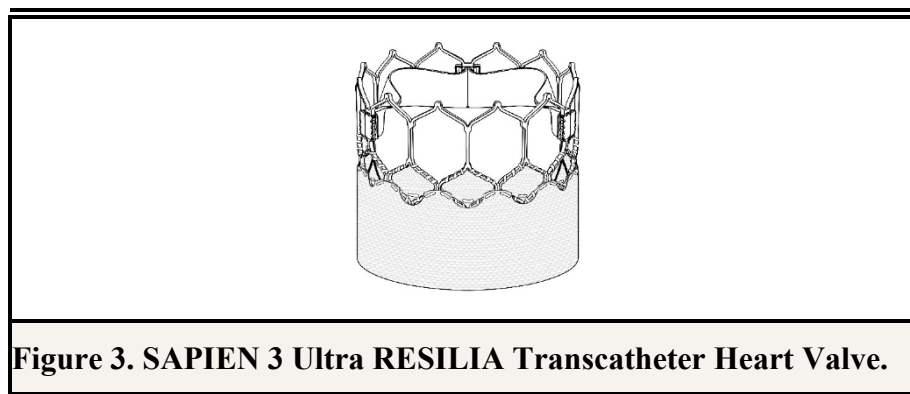
The Edwards SAPIEN 3 THV (model 9600TFX, 20, 23, 26, and 29 mm), as shown in Figure 1, is comprised of a balloon-expandable, radiopaque, cobalt-chromium (MP35N) frame, trileaflet bovine pericardial tissue valve, polyethylene terephthalate (PET) internal fabric skirt, and PET external sealing skirt for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



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.



The Edwards SAPIEN 3 Ultra RESILIA THV (model 9755RSL, 20, 23, 26, and 29 mm), as shown in Figure 3, is a design iteration of the SAPIEN 3 Ultra THV, with RESILIA bovine pericardial tissue leaflets.



The Edwards Commander delivery system (models 9600LDS20, 9600LDS23, 9600LDS26, 9600LDS29, 9750CM20, 9750CM23, 9750CM26, and 9750CM29), as shown in Figure 4,

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 uses the Edwards eSheath Introducer Set (models 914ES and 916ES) or Edwards eSheath+ introducer set (models 914ESP and 916ESP), which are off-the-shelf devices cleared under 510(k) K200258, to establish vascular access.

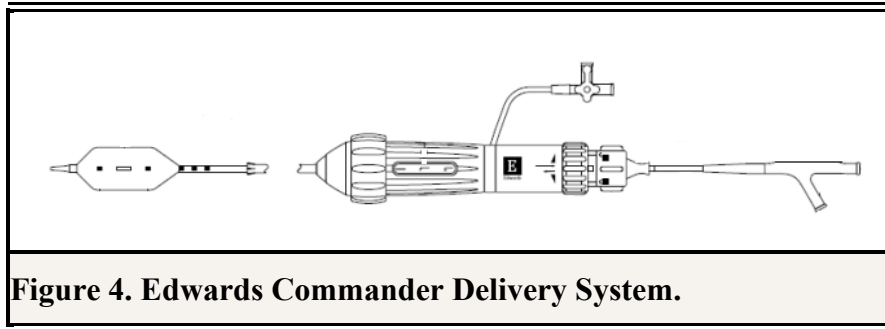


Figure 4. Edwards Commander Delivery System.

The Qualcrimp crimping accessory, as shown in Figure 5, 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.

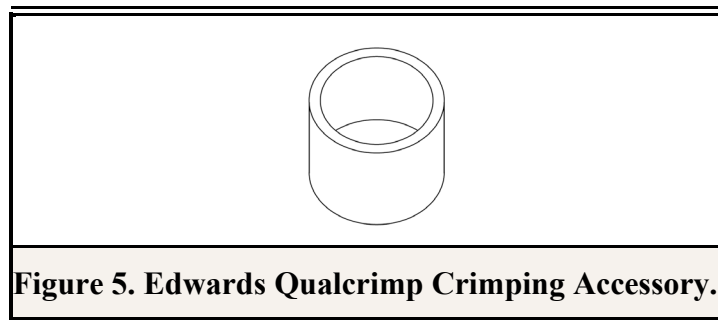


Figure 5. Edwards Qualcrimp Crimping Accessory.

The Edwards Crimper (model 9600CR), as shown in Figure 6, is comprised of various molded plastic components which compress the valve to a controlled aperture. The aperture is created by rotating the handle until it abuts the crimp stopper. The Edwards Crimper is used with a Crimp Stopper to correctly crimp the THV.

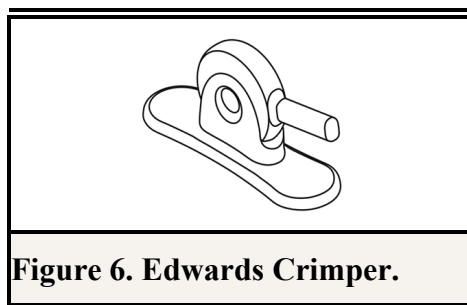


Figure 6. Edwards Crimper.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The alternative for the correction of asymptomatic severe native calcific aortic stenosis is SAVR. If intervention is not appropriate, clinical surveillance with regular follow-up is recommended, with medical therapy to manage risk factors. 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, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA THV system have not been marketed in the United States or any foreign country for transcatheter aortic valve replacement (TAVR) in patients with asymptomatic severe native calcific aortic stenosis.

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, atrium, septum, myocardium or valvular structures that may require intervention
- Pericardial effusion or cardiac tamponade
- Thoracic bleeding
- 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 or brachial plexus 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
- Left ventricular outflow tract (LVOT) obstruction
- 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 and SAPIEN 3 Ultra THV in patients with asymptomatic severe native calcific aortic stenosis under IDE G160259 (entitled the “EARLY TAVR” 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 RESILIA THV system was not used in the study. However, the results obtained on the Edwards SAPIEN 3 and SAPIEN 3 Ultra THV system are considered applicable to the Edwards SAPIEN 3 Ultra RESILIA THV system based on prior demonstration of device comparability in application P140031/S141.

A. Study Design

Patients were enrolled between July 2017 and December 2021. The database for this Panel Track PMA Supplement reflected data collected through April 1, 2024, and included 901 patients. There were 75 investigational sites in the US and Canada.

The EARLY TAVR trial was a prospective, randomized (1:1), controlled, multicenter study to compare TAVR with the Edwards SAPIEN 3 or SAPIEN 3 Ultra THV to clinical surveillance (CS).

The EARLY TAVR 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 study. The CEC adjudicated the events per Valve Academic Research Consortium-2 (VARC-2) definitions and some events were re-adjudicated per VARC-3 definitions.^{1,2} A biomarker core laboratory was used for assessment of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the EARLY TAVR trial was limited to patients who met the following inclusion criteria:

- 65 years of age or older at time of randomization
- Severe aortic stenosis defined as
 - Aortic valve area (AVA) $\leq 1.0 \text{ cm}^2$ or AVA index $\leq 0.6 \text{ cm}^2/\text{m}^2$ AND
 - Peak jet velocity $\geq 4.0 \text{ m/s}$ or mean gradient $\geq 40 \text{ mmHg}$
- Patient is asymptomatic defined as:
 - Negative treadmill stress test. To be considered asymptomatic, the patient must not demonstrate any of the following during and/or after the test:
 - Syncopal or pre-syncopal episode, including severe dizziness
 - Angina

- Limiting dyspnea or decreased exercise tolerance, defined as inability to reach 60% of age and sex adjusted metabolic equivalents of task (METs)
- Drop in systolic blood pressure (defined as a progressive drop of at least 20 mmHg and sustained for 1 minute or an acute drop of 40 mmHg)
- Significant ventricular arrhythmias (≥ 4 consecutive ventricular premature beats)

OR

- Per physician judgement after thorough assessment of patient history if the patient is unable to perform a stress test
- Left ventricular ejection fraction (LVEF) $\geq 50\%$
- Society of Thoracic Surgeons (STS) risk score ≤ 10
- 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) of the respective clinical site

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

- Patient is symptomatic (e.g., New York Heart Association [NYHA] Functional Class ≥ 2 , history of syncopal episode, or Canadian Cardiovascular Society angina score > 1 , hospitalization for heart failure within the last 12 months)
- Patient has any concomitant valvular, aortic, or coronary artery disease requiring surgery making aortic valve replacement (AVR) a Class I indication
- Native aortic annulus size unsuitable for sizes 20, 23, 26, or 29 mm THV based on 3-dimensional imaging analysis
- Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath
- LVOT calcification that would increase the risk of annular rupture or significant paravalvular leak (PVL) post-TAVR
- Evidence of an acute myocardial infarction ≤ 30 days before randomization
- Aortic valve is unicuspid, bicuspid with unfavorable features for TAVR (e.g., aneurysmal ascending aorta, i.e., > 4.0 cm; severe or bulky calcification of the LVOT or raphe that would increase the risk of annular injury or significant PVL post-TAVR; coronary anatomy that increases the risk of coronary artery obstruction post-TAVR), or is non-calcified
- Severe aortic regurgitation ($> 3+$)
- Severe mitral regurgitation ($> 3+$) or $\geq$ moderate mitral stenosis
- Pre-existing mechanical or bioprosthetic valve in any position (Note: mitral ring is not an exclusion.)
- Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of randomization
- Leukopenia (white blood cell < 3000 cell/mL), anemia (hemoglobin < 9 g/dL), thrombocytopenia (platelet count $< 50,000$ 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
- Cardiac imaging (echocardiogram, computed tomography, and/or magnetic resonance imaging) evidence of intracardiac mass, thrombus or vegetation
- Inability to tolerate or condition precluding treatment with anti-thrombotic therapy
- Stroke or transient ischemic attack (TIA) within 90 days of randomization
- Renal insufficiency (estimated glomerular filtration rate <30 mL/min per the Cockcroft-Gault formula) and/or renal replacement therapy
- Active bacterial endocarditis within 180 days of randomization
- Severe lung disease (forced expiratory volume in 1 second <50% predicted) or currently on home oxygen
- Severe pulmonary hypertension (e.g., pulmonary artery [PA] systolic pressure $\geq 2/3$ 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 aneurysm, severe calcification, aortic coarctation, etc.) that would preclude safe passage of the delivery system
- Patient refuses blood products
- Body mass index (BMI) $>50 \text{ kg/m}^2$
- Estimated life expectancy <24 months
- Absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with pre-medication
- 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.)
- Active SARS-CoV-2 infection (Coronavirus disease of 2019 [COVID-19]) or previously diagnosed with COVID-19 with sequelae that could confound endpoint assessments (as assessed by Case Review Board)

2. Follow-up Schedule

Follow-up periods for the TAVR cohort are discharge, 30-days, and 1-, 2-, 3-, and 5-years post-procedure. Follow-up periods for the CS cohort are 1-, 2-, 3-, and 5-years post-randomization. Patients in the CS cohort who undergo AVR during the 5-year follow-up period will be assessed per the TAVR cohort schedule, and those who remain asymptomatic and have not had AVR by the 5-year visit will be contacted by phone at 7 and 10 years to assess AVR status and survival. Preoperative and post-operative assessments included physical assessment, 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 death, all stroke, and unplanned cardiovascular hospitalization. Cardiovascular hospitalization was defined to be unplanned as follows:

- Admission through an emergency department or same day admission from a clinic; OR
- Any aortic valve intervention within 6 months of randomization in the CS cohort or aortic valve reintervention within 6 months of study procedure in the TAVR cohort

The analysis of the primary endpoint was a superiority comparison using the log-rank test to compare the survival curves. The hypothesis for the primary endpoint was as follows:

$$\begin{aligned}H_0: S_T(t) &= S_C(t) \\ H_A: S_T(t) &\neq S_C(t)\end{aligned}$$

where $S_T(t)$ and $S_C(t)$ represent the survival function at time t for the test cohort and control cohort, respectively. A two-sided log-rank test was performed using $\alpha=0.05$. The analysis was performed using all available data through 1825 days (i.e., 5 years) when the last patient reached the 2-year follow-up.

Once superiority was demonstrated for the primary endpoint, testing for superiority of TAVR as compared to CS was performed sequentially on 5 secondary endpoints in the order below:

- (1) Composite endpoint of being alive with a favorable KCCQ overall summary score at 2-year post-randomization visit. A favorable KCCQ overall summary score was defined as follows:
 - KCCQ overall summary score ≥ 75 and
 - KCCQ did not decrease by more than 10 points compared to baseline
- (2) Integrated left heart health at 2-year post-randomization visit:
 - Left ventricular (LV) longitudinal global strain $\geq 15\%$ and
 - LV mass index $< 115 \text{ g/m}^2$ for men or $< 95 \text{ g/m}^2$ for women and
 - Left atrial (LA) volume index ≤ 34
- (3) Change in LVEF at 2-year post-randomization visit
- (4) New onset atrial fibrillation
- (5) Death or disabling stroke

The hypothesis for endpoints (1) and (2) above was as follows:

$$\begin{aligned}H_0: R_T &= R_C \\ H_A: R_T &\neq R_C\end{aligned}$$

where R_T and R_C represent the success rate in the test cohort and control cohort,

respectively. The hypothesis was tested using a Fisher's exact test at a significance level of 0.05.

The hypothesis for endpoint (3) above was as follows:

$$H_0: D_T = D_C$$

$$H_A: D_T \neq D_C$$

where D_T and D_C denote the distribution of the change in LVEF from baseline in the test cohort and control cohort, respectively. The two cohorts were compared using the Wilcoxon rank-sum test at a two-sided α level of 0.05.

The hypothesis for endpoints (4) and (5) above was as follows:

$$H_0: S_T(t) = S_C(t)$$

$$H_A: S_T(t) \neq S_C(t)$$

where $S_T(t)$ and $S_C(t)$ represent the survival function at time t for the test cohort and control cohort, respectively. A two-sided log-rank test was performed using a significance level of 0.05.

A gatekeeping method was used to control the overall type I error between the primary and secondary endpoints. A mixture of hierarchical gatekeeping and the Hochberg method were used to control the type I error of 0.05 within the secondary endpoints.^{3,4}

B. Accountability of the PMA Cohort

At the time of database extract, a total of 901 patients were randomized in the study. The analysis populations included Intention-to-Treat (ITT) and Valve Implant (VI), as defined in Table 1. The primary endpoint analysis was the ITT analysis.

Table 1. Analysis Populations			
Analysis Population	Definition	Number of Patients	
		TAVR	CS
Intention-To-Treat (ITT)	All randomized patients.	455	446
Valve Implant (VI)	All patients who received and retained a replacement aortic valve (a study valve or a non-study valve) upon leaving the procedural room.	444	388

TAVR: transcatheter aortic valve replacement; CS: clinical surveillance.

The VI population that originated from the CS population constitutes the delayed AVR (DAVR) cohort.

The follow-up compliance at 2 years post-randomization is summarized in Table 2.

Table 2. Overall Study Compliance (ITT Population)		
Patient Accountability	2-Year Visit*	
	TAVR (N=455)	CS (N=446)
Total patients	455	446
Non-eligible	31	25
Death	17	12
Withdrawal	10	11
Lost to follow-up	0	0
Termination by investigator	1	2
Exit with other reason	3	0
Visit not yet due	0	0
Eligible	424	421
Follow-up visit completed	98.6% (418)	98.3% (414)
Visit not completed	1.4% (6)	1.7% (7)

*2-year visit is post-procedure for the TAVR cohort and post-randomization for the CS cohort.

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 study cohorts were generally well balanced.

Table 3. Patient Demographics and Baseline Characteristics (ITT Population)		
Demographics and Baseline Characteristics	Summary Statistics*	
	TAVR (N=455)	CS (N=446)
Age - years	76.0 ± 6.03	75.6 ± 5.97
Male sex	71.2% (324/455)	67.0% (299/446)
Hispanic or Latino Ethnicity	2.4% (11/455)	2.0% (9/446)
Race		
American Indian or Alaska Native	0.0% (0/455)	0.0% (0/446)
Asian	1.5% (7/455)	2.0% (9/446)

Demographics and Baseline Characteristics	Summary Statistics*	
	TAVR (N=455)	CS (N=446)
Black or African American	2.0% (9/455)	2.5% (11/446)
Native Hawaiian or other Pacific Islander	0.0% (0/455)	0.0% (0/446)
White	95.8% (436/455)	94.6% (422/446)
Multiple races	0.4% (2/455)	0.4% (2/446)
Unknown	0.2% (1/455)	0.4% (2/446)
Society of Thoracic Surgeons (STS) score	1.8 ± 1.00 (455)	1.7 ± 0.96 (446)
Able to perform treadmill stress test	90.3% (411/455)	90.8% (405/446)
Biomarker – NT-proBNP (pg/mL) †	275.6 (138.8, 598.9) (414)	296.8 (147.6, 607.7) (384)
New York Heart Association (NYHA) class		
I	100.0% (455/455)	100.0% (446/446)
Previous myocardial infarction	5.1% (23/455)	4.0% (18/446)
Previous intervention		
Coronary artery bypass grafting (CABG)	5.9% (27/455)	6.5% (29/446)
Percutaneous coronary intervention (PCI)	18.0% (82/455)	13.9% (62/446)
Stroke	4.2% (19/455)	4.5% (20/446)
Peripheral vascular disease (PVD)	7.3% (33/455)	4.7% (21/446)
Atrial fibrillation	15.6% (71/455)	13.2% (59/446)
Atrial flutter	2.9% (13/455)	3.4% (15/446)
Permanent pacemaker or defibrillator	4.6% (21/455)	2.0% (9/446)
Echocardiographic findings		
Aortic valve area (cm ²)	0.9 ± 0.23 (436)	0.8 ± 0.23 (425)
Aortic valve mean gradient (mmHg)	46.5 ± 10.08 (451)	47.3 ± 10.61 (442)
Left ventricular ejection fraction (LVEF) (%)	67.4 ± 6.54 (451)	67.4 ± 6.68 (444)
Moderate or severe aortic regurgitation	2.2% (10/449)	3.2% (14/441)
Moderate or severe mitral regurgitation	1.3% (6/448)	1.8% (8/435)

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

† Continuous measures (NT-proBNP) – Median (Q1, Q3) (Total no.)

D. Safety and Effectiveness Results

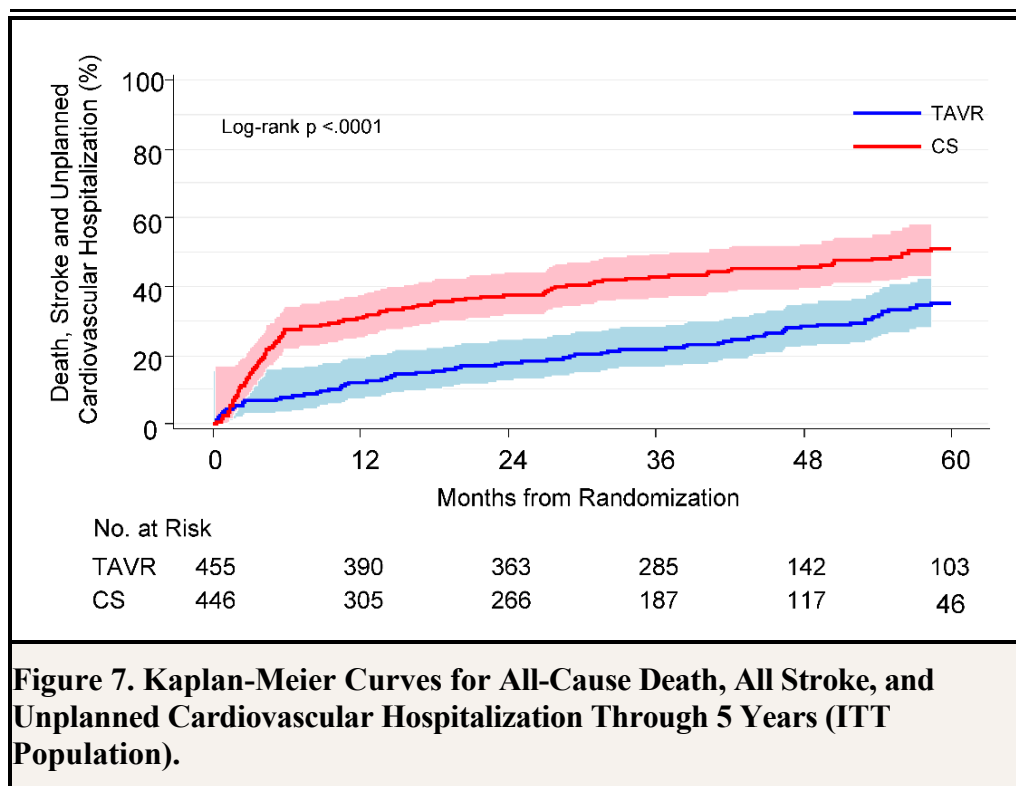
1. Primary Endpoint

The primary endpoint results are presented in Table 4 and Figure 7. During a median follow-up of 3.8 years, a primary endpoint event occurred in 122 patients (26.8%) in the TAVR cohort and in 202 patients (45.3%) in the CS cohort, with a p-value of <0.0001. Superiority of the TAVR cohort compared to the CS cohort was achieved, driven primarily by unplanned cardiovascular hospitalization, especially aortic valve intervention within 6 months of randomization in the CS cohort.

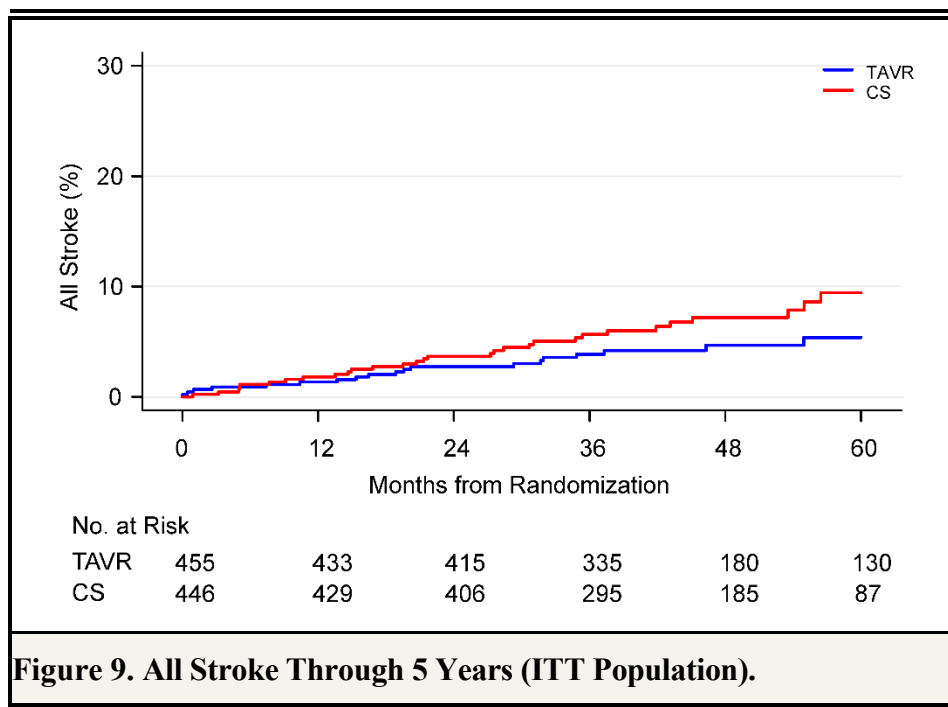
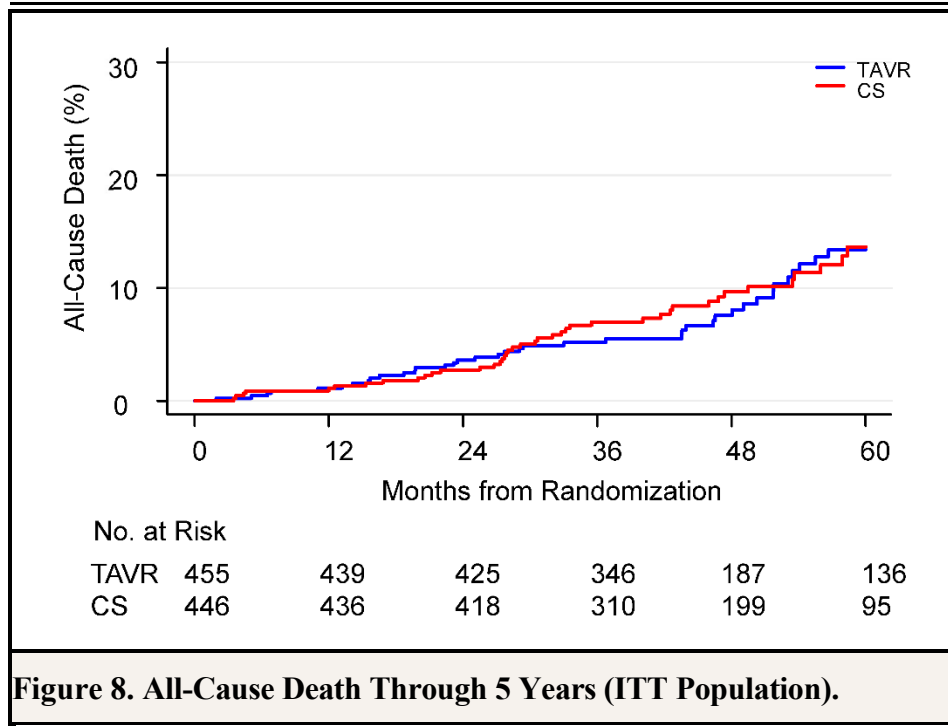
Table 4. Primary Endpoint Analysis (ITT Population)				
Event	Summary Statistics*		P-value†	Pass/Fail
	TAVR (N=455)	CS (N=446)		
Composite of all-cause death, all stroke, and unplanned cardiovascular hospitalization	122 (26.8%)	202 (45.3%)	<0.0001	Pass
All-cause death	38 (8.4%)	41 (9.2%)	-	-
All stroke	19 (4.2%)	30 (6.7%)	-	-
Unplanned cardiovascular hospitalization	95 (20.9%)	186 (41.7%)	-	-
Admission through an emergency department or same day admission from a clinic	94 (20.7%)	107 (24.0%)	-	-
Aortic valve intervention/reintervention within 6 months	2 (0.4%)	116 (26.0%)	-	-

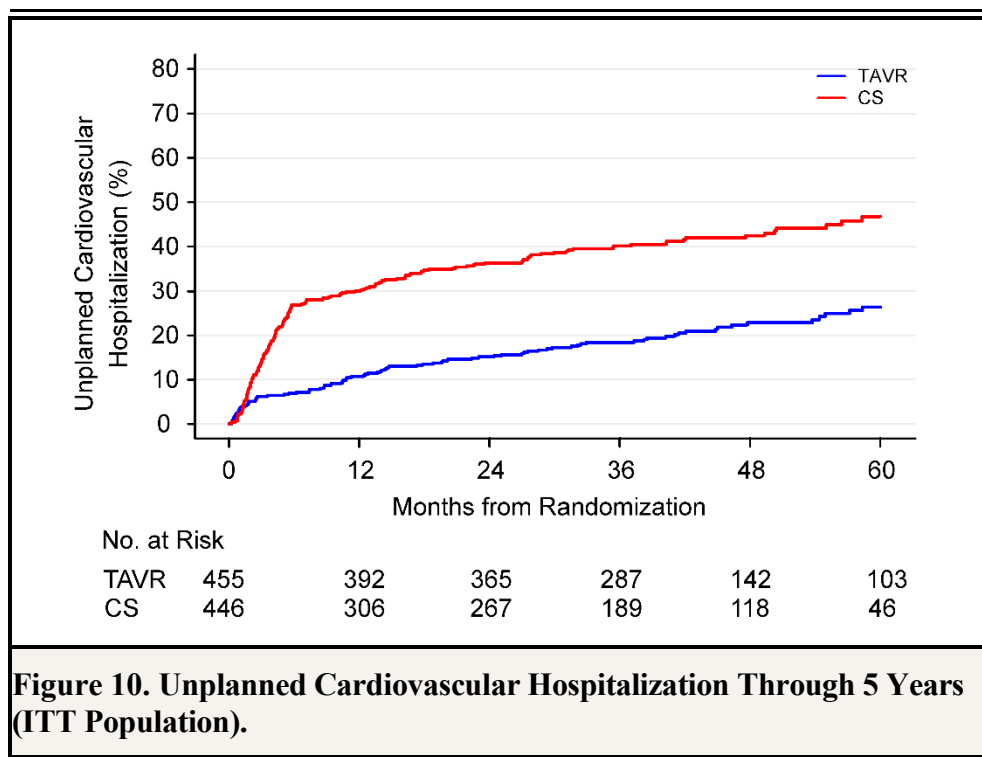
* no. of patients with the event (%). Reference start date for ITT population is randomization date.

†P-value is from log-rank test of all available data through 1825 days (i.e., 5 years).



The times to first event for each of the primary endpoint components are shown in Figure 8 through Figure 10.





2. Secondary Endpoints

Since the primary endpoint passed superiority testing, prespecified superiority testing was carried out on 5 secondary endpoints sequentially, as summarized in Table 5. The secondary endpoints for the composite of being alive with a favorable KCCQ overall summary score and integrated measure of LV health were met. However, there was no significant difference in the change in LVEF at 2 years between the TAVR and CS cohorts. Thus, hypothesis testing was not performed for the remaining endpoints on the hierarchical list.

Table 5. Superiority Testing of Secondary Endpoints (ITT Population)					
No.	Endpoint	Summary Statistics*		P-value	Test Result
		TAVR (N=455)	CS (N=446)		
1	Composite of being alive with a favorable KCCQ overall summary score at 2 years	86.6% (354/409)	68.0% (266/391)	<0.0001	Pass
2	Integrated measure of left heart health at 2 years	48.1% (180/374)	35.9% (121/337)	0.0011	Pass

No.	Endpoint	Summary Statistics*		P-value	Test Result
		TAVR (N=455)	CS (N=446)		
3	Change in LVEF at 2 years	-1.2 ± 0.40 (393)	-1.3 ± 0.39 (355)	0.6637	Fail
4	New onset atrial fibrillation [†]	13.0% (50)	12.4% (48)	-	-
5	Death or disabling stroke	9.7% (44)	11.2% (50)	-	-

KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: left ventricular ejection fraction.

*Continuous measures – mean ± SE (n); Categorical measures – % (no./Total no.); Time to event measures - % (no. of patients with the event). Reference start date for ITT population is randomization date.

[†]New onset atrial fibrillation is only estimated among those without atrial fibrillation at baseline.

3. Adverse Events

The Kaplan-Meier estimates of CEC-adjudicated adverse events through 2 years are presented in Table 6.

Table 6. CEC-Adjudicated Adverse Events Through 2 Years (ITT Population)				
Event	Kaplan-Meier Estimate*			
	1 Year		2 Years	
	TAVR (N=455)	CS (N=446)	TAVR (N=455)	CS (N=446)
All-cause death	1.1% (5, 5)	1.1% (5, 5)	3.6% (16, 16)	2.7% (12, 12)
Cardiovascular death	0.9% (4, 4)	0.7% (3, 3)	2.7% (12, 12)	1.8% (8, 8)
All stroke	1.3% (6, 6)	1.8% (8, 8)	2.7% (12, 12)	3.7% (17, 16)
Disabling stroke	0.0% (0, 0)	0.7% (3, 3)	0.9% (4, 4)	1.6% (7, 7)
Non-disabling stroke	1.3% (6, 6)	1.1% (5, 5)	1.8% (8, 8)	2.1% (10, 9)
Death or stroke	2.5% (11, 11)	2.9% (13, 13)	5.9% (28, 26)	5.7% (29, 25)
Death or disabling stroke	1.1% (5, 5)	1.8% (8, 8)	4.1% (20, 18)	3.9% (19, 17)
Hospitalization	22.7% (139, 101)	50.5% (301, 223)	33.7% (238, 149)	76.1% (515, 333)
Cardiovascular	11.4% (67, 51)	48.3% (252, 213)	17.0% (103, 75)	73.0% (406, 319)

Event	Kaplan-Meier Estimate*			
	1 Year		2 Years	
	TAVR (N=455)	CS (N=446)	TAVR (N=455)	CS (N=446)
Non-cardiovascular	12.6% (72, 56)	8.6% (49, 38)	21.8% (135, 96)	17.2% (109, 75)
New permanent pacemaker†	7.2% (31, 31)	3.3% (16, 14)	8.2% (35, 35)	7.3% (33, 31)
Myocardial infarction	1.1% (5, 5)	0.9% (4, 4)	1.8% (9, 8)	1.4% (6, 6)

*Kaplan-Meier estimate - % (no. of events, no. of patients with the event). Reference start date for ITT population is randomization date.

†New pacemaker was only estimated among those without pacemaker at baseline.

4. Subgroup Analyses

The results of the prespecified subgroup analyses on sex, STS score, ability to perform the treadmill stress test, and aortic valve peak velocity are presented in Figure 11. The study was not specifically powered for any subgroup.

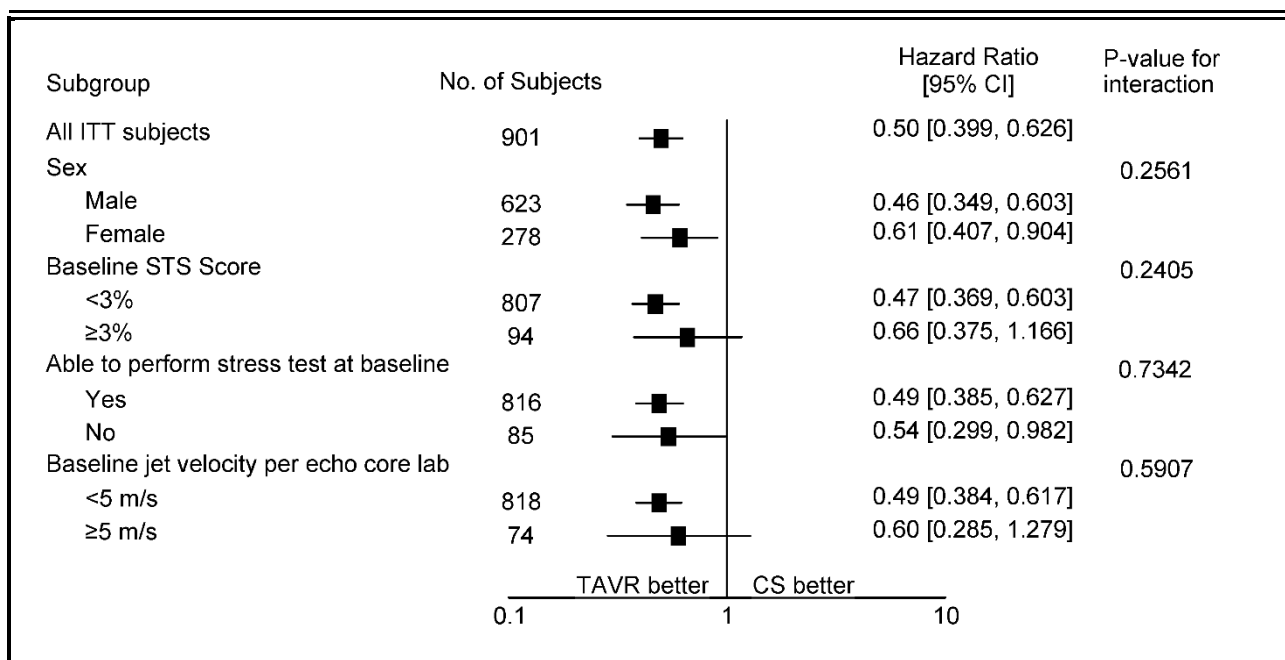
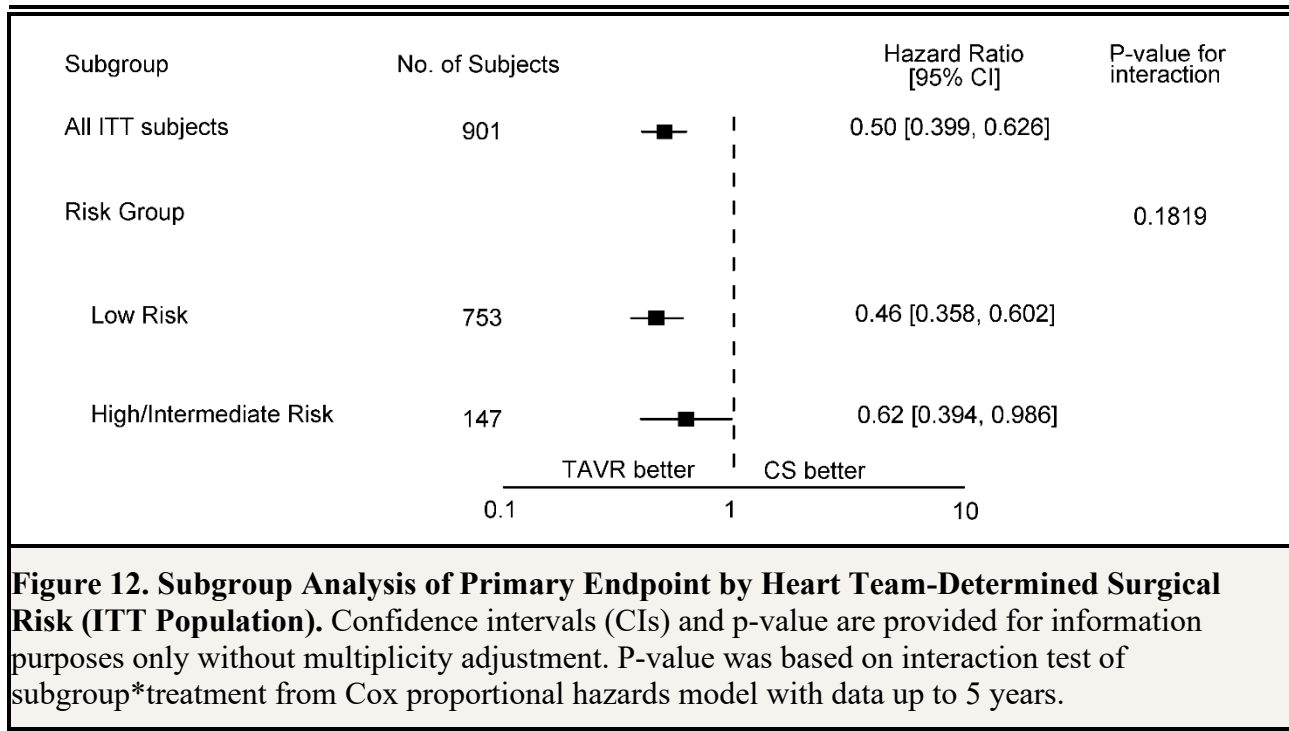


Figure 11. Subgroup Analyses of Primary Endpoint by Sex, STS Score, Ability to Perform Treadmill Stress Test, and Aortic Valve Peak Velocity (ITT Population). Confidence intervals (CIs) and p-values are provided for information purposes only without multiplicity adjustment. P-values were based on interaction test of subgroup*treatment from Cox proportional hazards model with data up to 5 years.

The majority (83.6%) of patients randomized were deemed to be at low surgical risk as evaluated by the local heart team. The results of a *post hoc* subgroup analysis of the primary endpoint by heart team-determined surgical risk are shown in Figure 12.



The primary endpoint result by race is shown in Table 7.

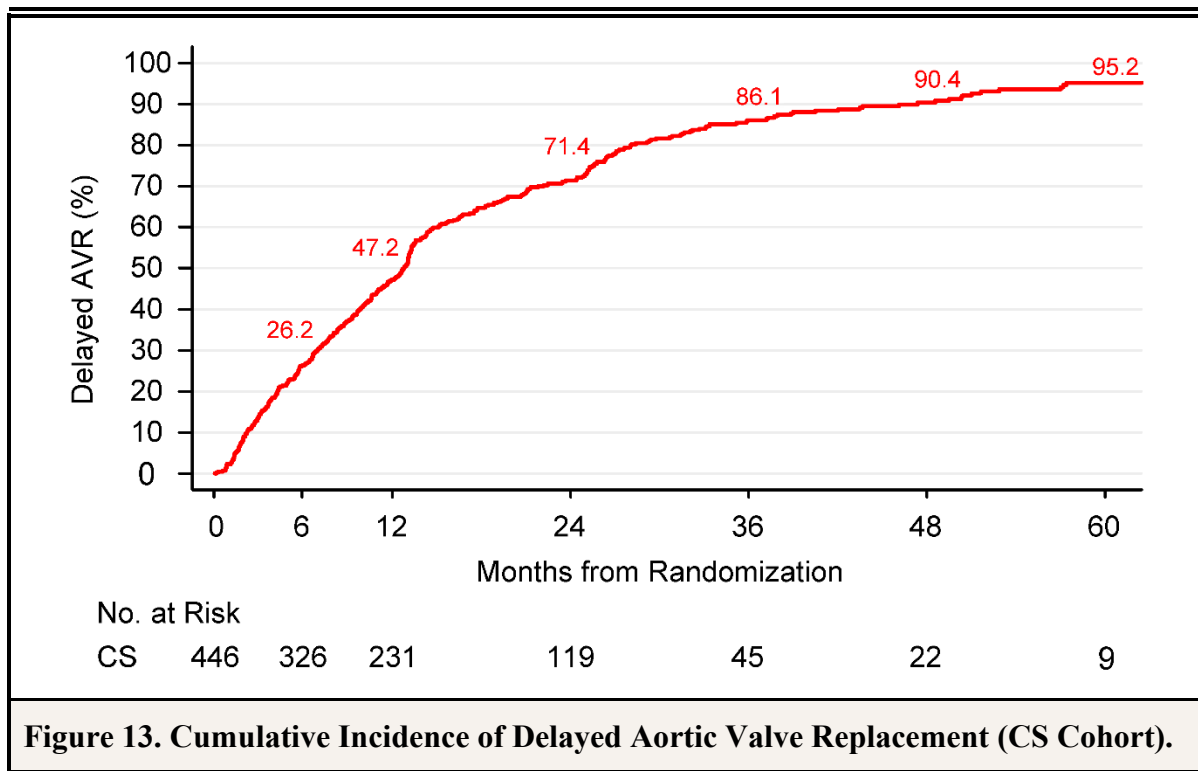
Table 7. Primary Endpoint Result by Race (ITT Population)		
Race	Composite of All-cause Death, All Stroke, and Unplanned Cardiovascular Hospitalization *	
	TAVR	CS
American Indian or Alaska Native	0/0	0/0
Asian	2/7	5/9
Black or African American	2/9	5/11
Native Hawaiian or other Pacific Islander	0/0	0/0
White	116/436	191/422
Multiple	2/2	0/2
Unknown	0/1	1/2

* no. of patients with events/total no. patients in the subgroup.

5. VI Population Analyses

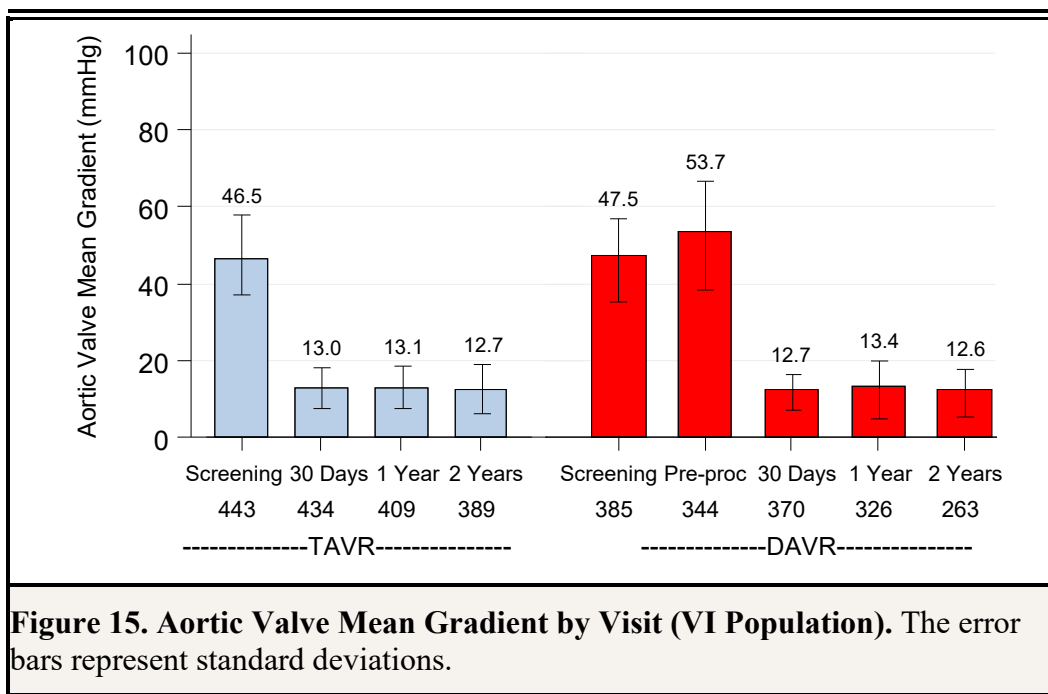
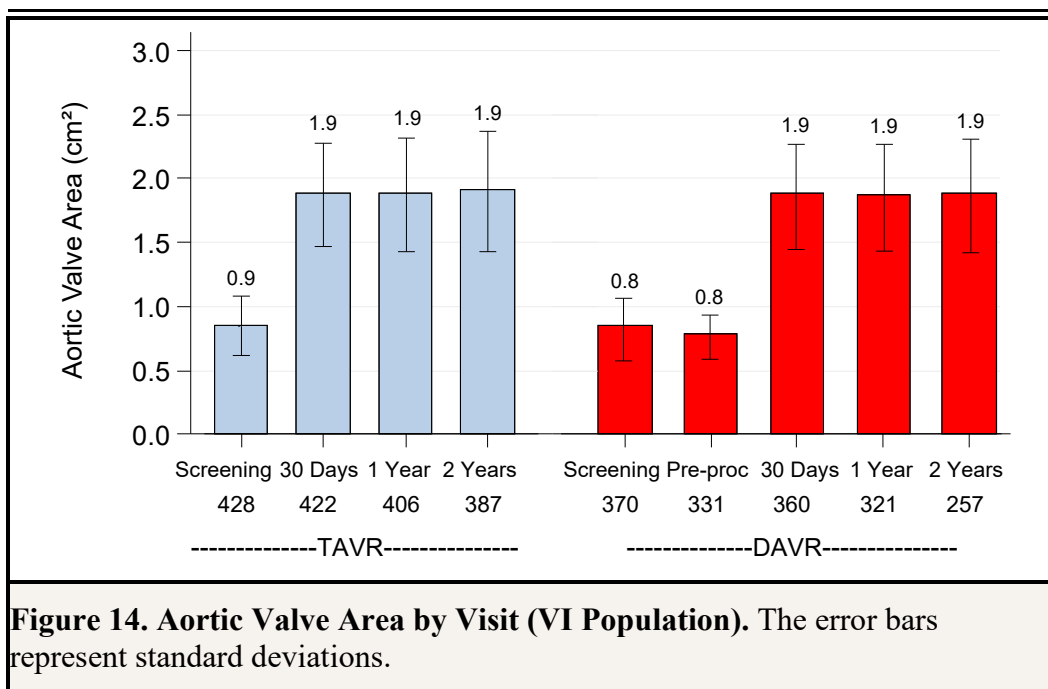
Conversion to AVR

The Kaplan-Meier estimates for the incidence of DAVR post randomization in the CS cohort are presented in Figure 13. By 12 months post randomization, 47.2% of the patients in the CS cohort became symptomatic and underwent AVR. The median time to DAVR was 332.5 days.



Valve Performance

The effective orifice area (EOA), mean aortic gradient, total aortic regurgitation (AR), and paravalvular regurgitation values obtained over time for the TAVR cohort and DAVR cohort patients are summarized in Figure 14 through Figure 17, respectively. Hemodynamic results at screening were similar between the two cohorts, remained unchanged (aortic valve area) or declined (aortic valve mean gradient) in the DAVR cohort pre-procedure, and improved similarly in both cohorts post-procedure through 2 years.



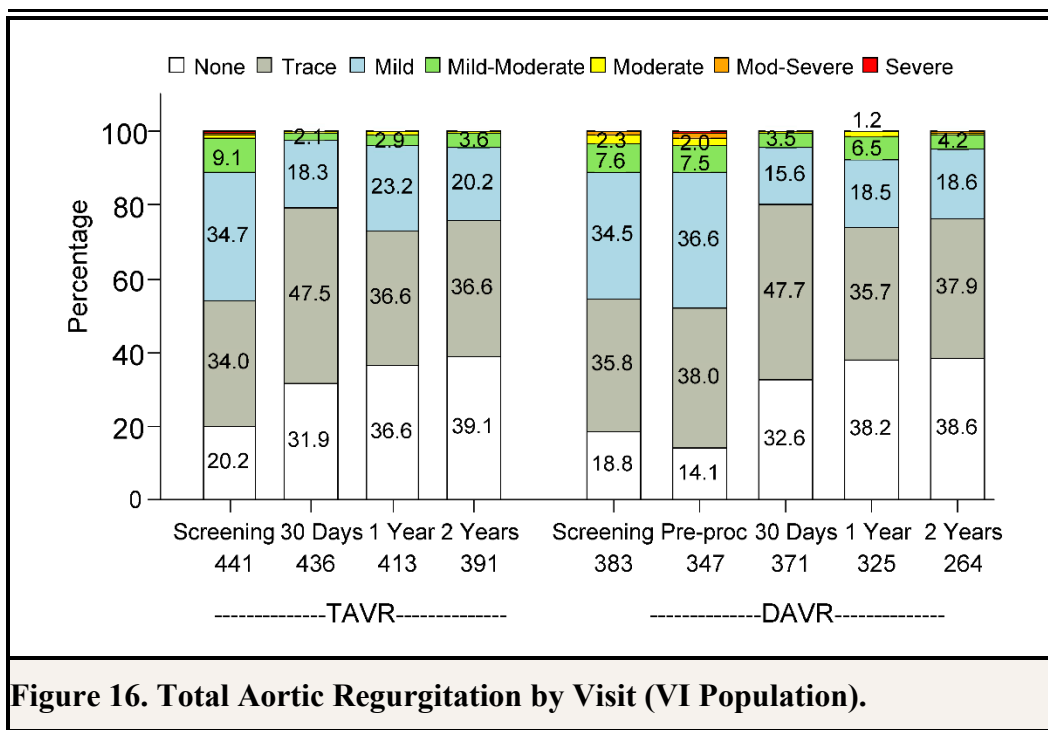


Figure 16. Total Aortic Regurgitation by Visit (VI Population).

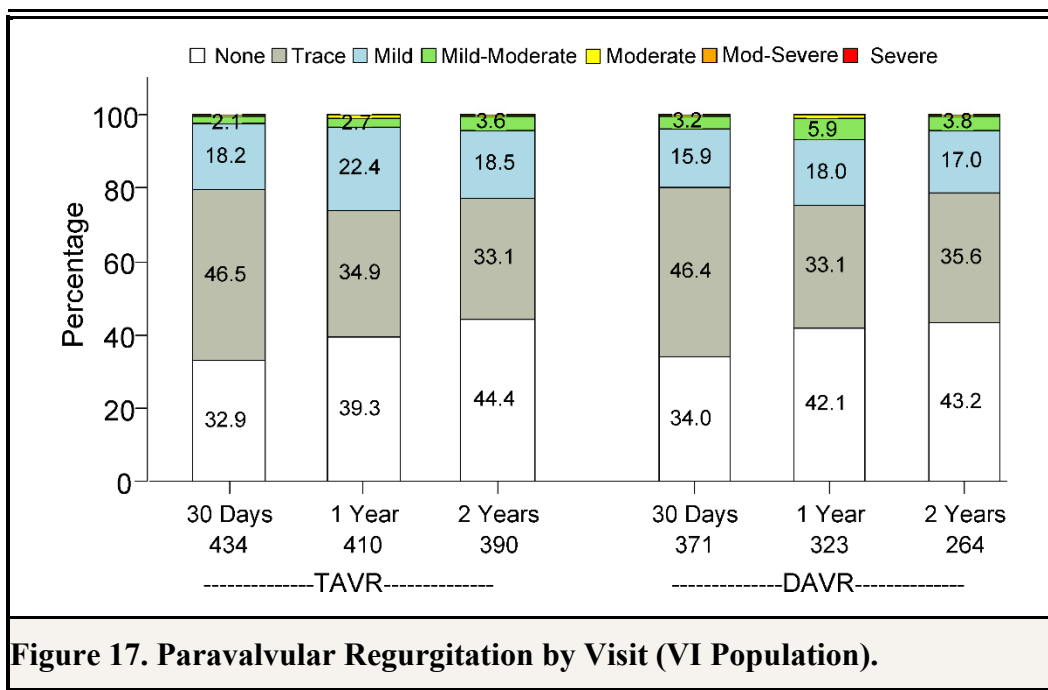
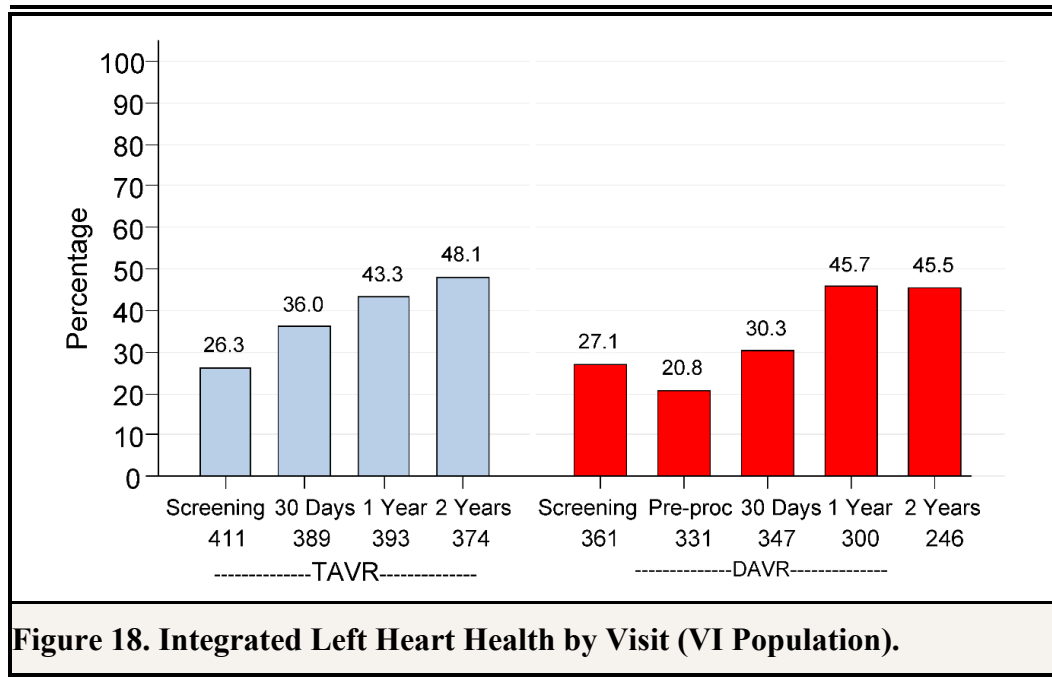


Figure 17. Paravalvular Regurgitation by Visit (VI Population).

Integrated Left Heart Health

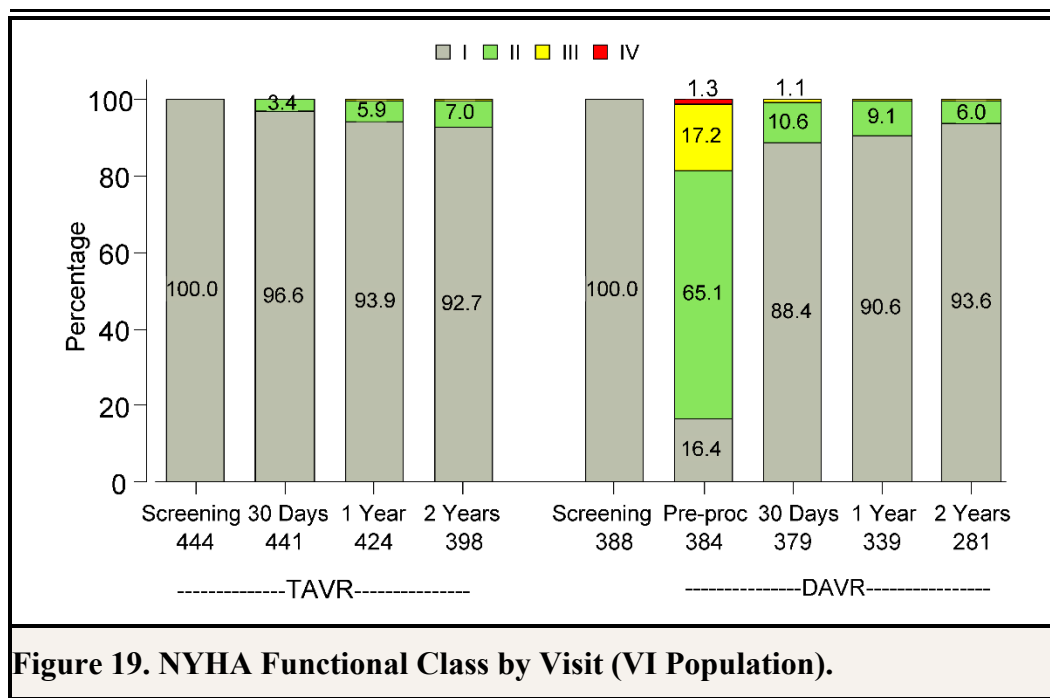
The proportions of patients in the two study cohorts with a healthy integrated left heart function are shown in Figure 18. The results were similar at screening between the two

cohorts, declined in the CS cohort prior to DAVR, and improved in both cohorts after the procedure, with similar rates seen through 2 years.



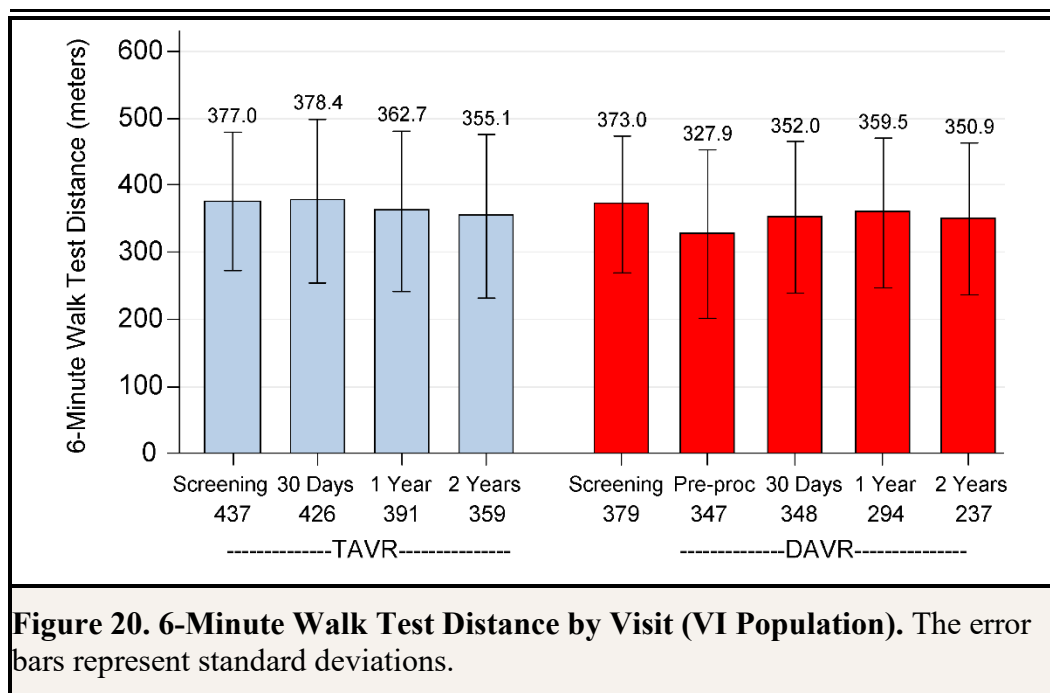
NYHA Functional Class

The NYHA classifications by visit are presented in Figure 19. The majority of patients (>90%) in the TAVR cohort remained in NYHA class I at all follow-up visits through 2 years. In contrast, in the CS cohort, a decline in NYHA class was seen pre-procedure with the majority of patients (83.6%) becoming symptomatic (NYHA >1). After DAVR, the NYHA class improved and the outcomes at 2 years were similar between the two cohorts.



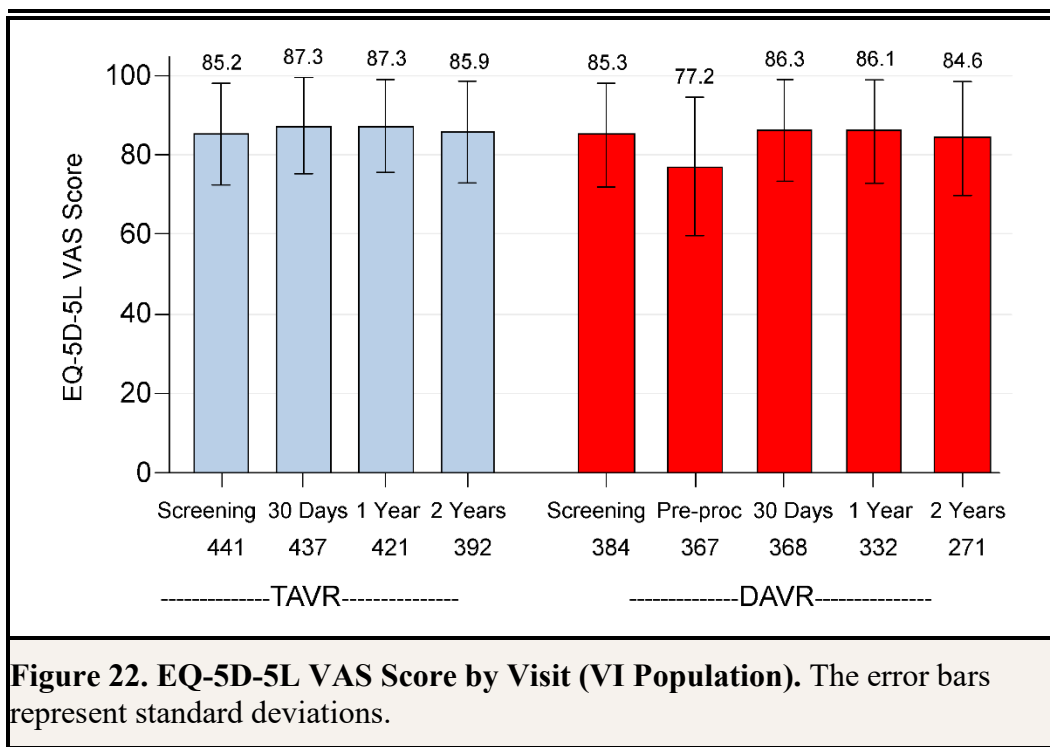
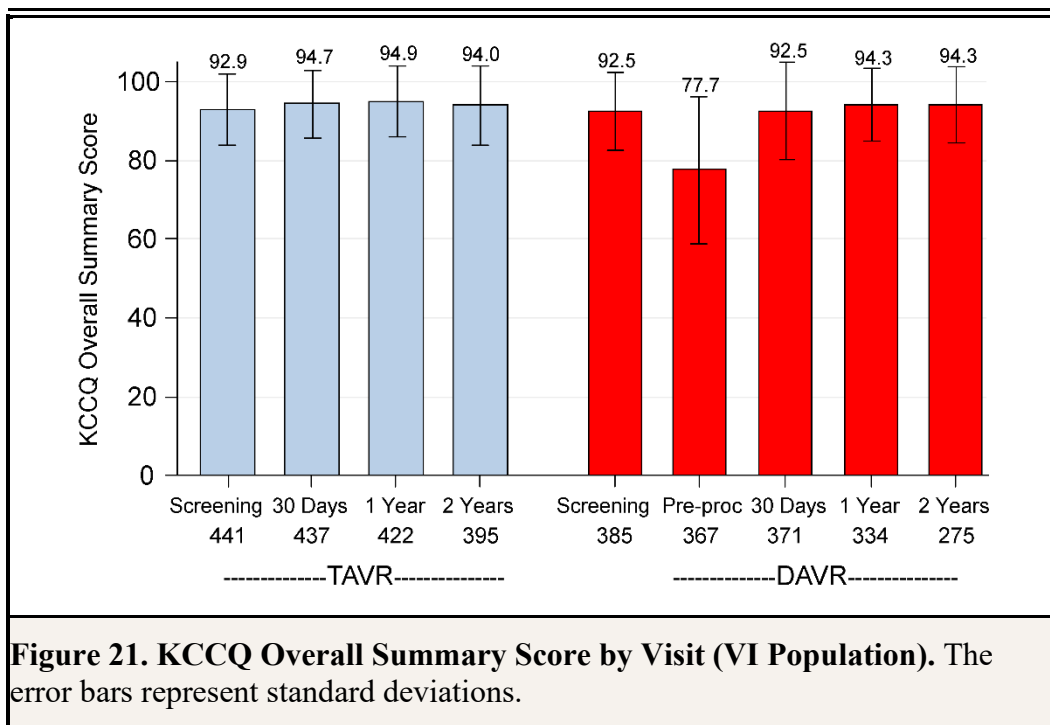
6-Minute Walk Test (6MWT)

The results for the 6MWT distance are presented in Figure 20. The mean walk distances at screening were similar between the TAVR cohort and the DAVR cohort. However, the mean walk distance in the DAVR cohort decreased by about 45 meters pre-procedure and improved by about 24 meters post-procedure, with similar distances between the two cohorts at 2 years (355.1 vs. 350.9 meters).

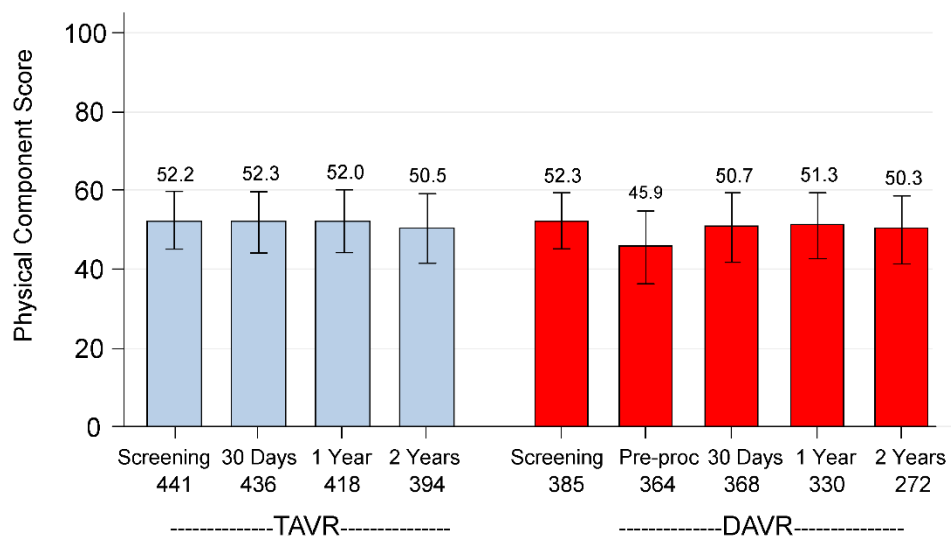


Health Status

The results for the KCCQ overall summary score, EQ-5D-5L VAS score, and Short Form (SF)-36 summary scores are shown in Figure 21 through Figure 23, respectively. There is a common trend in the KCCQ overall summary score, EQ-5D-5L VAS score, and SF-36 physical component summary score; these scores were similar between the two cohorts at screening. They remained mostly stable through 2 years in the TAVR cohort while seeing a decline prior to DAVR and then a return to the screening values post DAVR in the CS cohort. For example, the mean KCCQ overall summary scores at screening were similar between the TAVR cohort and the DAVR cohort (92.9 vs. 92.5). Patients in the TAVR cohort maintained the high score through 2 years post-procedure. In contrast, patients in the DAVR cohort first saw a clinically significant decline in the score to 77.7 pre-procedure and then a recovery to 92.5 post-procedure, which remained mostly unchanged through 2 years post-procedure.



A. Physical Component



B. Mental Component

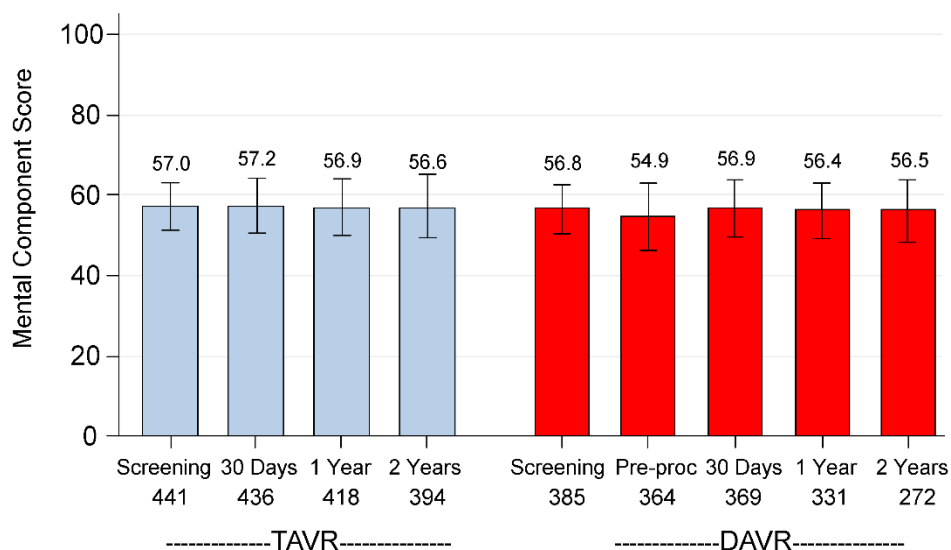
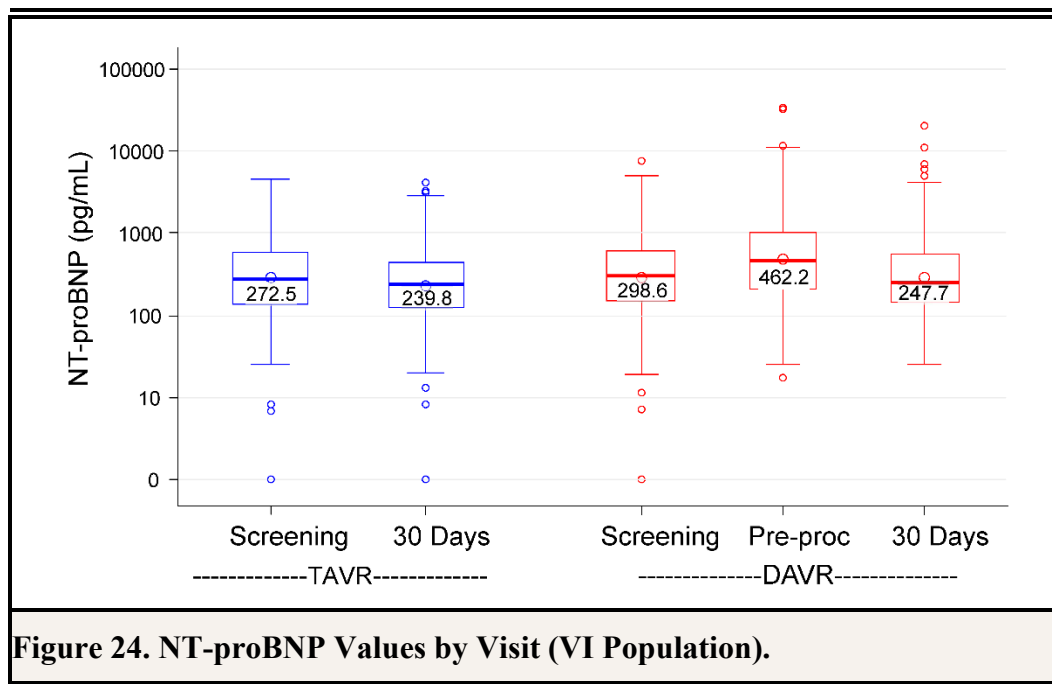


Figure 23. SF-36 Summary Score by Visit (VI Population). The error bars represent standard deviations.

NT-proBNP Assessment

The NT-proBNP results are shown in Figure 24. Compared to the results at screening, the TAVR cohort saw a slight reduction in median NT-proBNP level from 272.5 pg/mL to 239.8 pg/mL at 30 days post-procedure, while the CS cohort saw an increase in median NT-proBNP level from 298.6 pg/mL to 462.2 pg/mL prior to DAVR and then a decrease to a level (247.7 pg/mL) closer to the screening value post-procedure.



Safety Endpoints

The Kaplan-Meier estimates of the CEC-adjudicated safety endpoints for the VI population through 2 years are presented in Table 8.

Table 8. CEC-Adjudicated Safety Endpoints Through 2 Years (VI Population)						
Event	Kaplan-Meier Estimate*					
	30 Days		1 Year		2 Years	
	TAVR (N=444)	DAVR (N=388)	TAVR (N=444)	DAVR (N=388)	TAVR (N=444)	DAVR (N=388)
All-cause death	0.2% (1, 1)	0.0% (0, 0)	1.1% (5, 5)	2.2% (8, 8)	3.8% (17, 17)	5.6% (19, 19)
Cardiovascular death	0.0% (0, 0)	0.0% (0, 0)	0.9% (4, 4)	1.1% (4, 4)	3.0% (13, 13)	3.3% (11, 11)

Event	Kaplan-Meier Estimate*					
	30 Days		1 Year		2 Years	
	TAVR (N=444)	DAVR (N=388)	TAVR (N=444)	DAVR (N=388)	TAVR (N=444)	DAVR (N=388)
All stroke	0.9% (4, 4)	1.8% (8, 7)	1.4% (6, 6)	2.6% (11, 10)	2.7% (12, 12)	4.5% (18, 16)
Disabling stroke	0.0% (0, 0)	1.0% (4, 4)	0.0% (0, 0)	1.3% (5, 5)	0.9% (4, 4)	2.2% (8, 8)
Non-disabling stroke	0.9% (4, 4)	0.8% (4, 3)	1.4% (6, 6)	1.3% (6, 5)	1.8% (8, 8)	2.3% (10, 8)
Death or stroke	1.1% (5, 5)	1.8% (8, 7)	2.5% (11, 11)	4.2% (19, 16)	6.1% (29, 27)	8.9% (37, 31)
Death or disabling stroke	0.2% (1, 1)	1.0% (4, 4)	1.1% (5, 5)	3.2% (13, 12)	4.3% (21, 19)	6.9% (27, 24)
Hospitalization	6.1% (27, 27)	8.6% (36, 33)	21.9% (136, 97)	22.8% (114, 85)	33.5% (241, 148)	33.5% (186, 119)
Cardiovascular	4.7% (21, 21)	6.7% (27, 26)	11.1% (65, 49)	12.7% (51, 48)	16.6% (102, 73)	17.5% (73, 63)
Non-cardiovascular	1.4% (6, 6)	2.1% (9, 8)	12.2% (71, 54)	13.8% (63, 51)	22.3% (139, 98)	23.4% (113, 81)
New permanent pacemaker†	5.7% (24, 24)	8.4% (33, 32)	7.1% (30, 30)	9.8% (39, 37)	8.3% (35, 35)	10.4% (41, 39)
Myocardial infarction	0.5% (2, 2)	0.5% (2, 2)	1.1% (5, 5)	0.5% (2, 2)	1.8% (9, 8)	1.1% (4, 4)
Major vascular complications	1.4% (6, 6)	1.0% (5, 4)	-	-	-	-
Bleeding complications	12.8% (63, 57)	13.7% (58, 53)	-	-	-	-
Acute kidney injury‡	2.5% (11, 11)	3.4% (13, 13)	-	-	-	-
Coronary obstruction requiring intervention	0.0% (0, 0)	0.0% (0, 0)	-	-	-	-

*Kaplan-Meier estimate – % (no. of events, no. of patients with the event). Reference start date for VI population is procedure date.

†New pacemaker was only estimated among those without pacemaker at baseline (for DAVR patients, “baseline” means pre-procedure visit).

‡Acute kidney injury was from site reported data.

6. Other Study Observations

Procedural Information

The procedural data for the TAVR and DAVR cohorts are summarized in Table 9. The procedural characteristics were generally comparable between the two cohorts with the exception of a higher percentage of SAPIEN 3 Ultra valves implanted in the DAVR cohort due to the commercial approval of this device later in the study.

Table 9. Procedure Data (VI Population)		
Variable	Summary Statistics*	
	TAVR (N=444)	DAVR (N=388)
Anesthesia type		
General anesthesia	18.9% (84/444)	18.8% (73/388)
Conscious sedation	80.0% (355/444)	80.2% (311/388)
Conversion from conscious sedation to general anesthesia	1.1% (5/444)	1.0% (4/388)
Anesthesia duration (min)	117.2 ± 2.19 (444)	119.2 ± 2.40 (386)
Procedure duration (min)	40.0 ± 0.84 (443)	45.0 ± 2.02 (380)
Total fluoroscopy time (min) [†]	12.8 ± 0.31 (442)	13.8 ± 0.35 (374)
Balloon aortic valvuloplasty performed [†]	28.2% (125/444)	33.6% (128/381)
Final valve type		
SAPIEN 3	81.3% (361/444)	55.4% (215/388)
SAPIEN 3 Ultra	18.7% (83/444)	40.2% (156/388)
Non-study transcatheter heart valve (THV)	-	2.6% (10/388)
Surgical valve	-	1.8% (7/388)
Study valve size		
20 mm	3.2% (14/444)	0.8% (3/371)
23 mm	28.6% (127/444)	34.8% (129/371)
26 mm	48.9% (217/444)	45.8% (170/371)
29 mm	19.4% (86/444)	18.6% (69/371)
Post dilatation performed [†]	14.0% (62/444)	13.7% (52/380)
Cerebral protection device used	21.6% (96/444)	26.8% (102/381)

Variable	Summary Statistics*	
	TAVR (N=444)	DAVR (N=388)
More than one THV implanted [†]	0.9% (4/444)	0.5% (2/381)

* Continuous measures – mean ± SE (n); Categorical measures – % (no./total no.).

[†]Only reported among those with TAVR procedure.

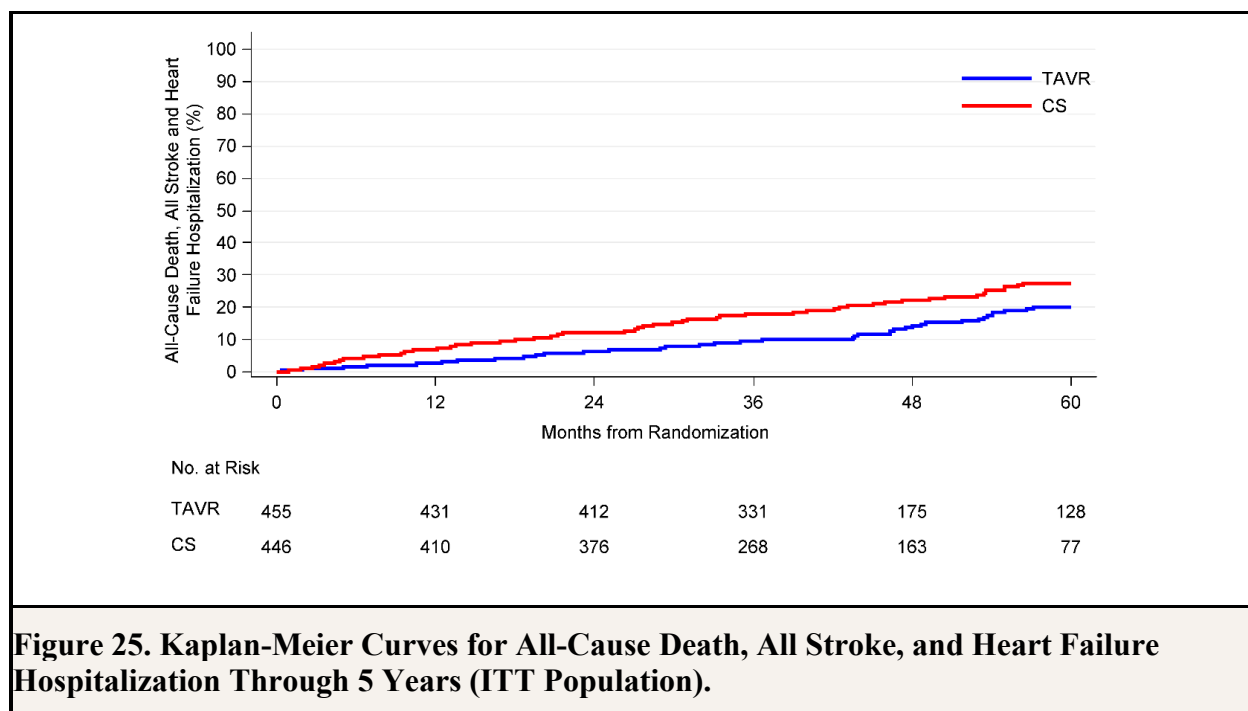
Composite of All-Cause Death, All Stroke, or Heart Failure Hospitalization

A *post hoc* exploratory analysis for the composite of all-cause death, all stroke, or heart failure hospitalization is presented in Table 10 and Figure 25. There appears to be a lower incidence of composite event of all-cause death, all stroke, or heart failure hospitalization through 5 years in the TAVR cohort than in the CS cohort (13.6% vs. 21.3%).

Table 10. All-Cause Death, All Stroke, or Heart Failure Hospitalization Through 5 Years (ITT Population).		
Event	Summary Statistics*	
	TAVR (N=455)	CS (N=446)
Composite of all-cause death, all stroke, or heart failure hospitalization	62 (13.6%)	95 (21.3%)
All-cause death	38 (8.4%)	41 (9.2%)
All stroke	19 (4.2%)	30 (6.7%)
Heart failure hospitalization [†]	15 (3.3%)	44 (9.9%)

* no. of patients with the event (%). Reference start date for ITT population is randomization date.

[†]Heart failure hospitalization was defined as hospitalization for symptoms of congestive heart failure and administration of intravenous diuresis or inotropic therapy, institution of mechanical support, or hemodialysis and was adjudicated by the CEC.



7. Pediatric Extrapolation

In this premarket application, existing clinical data were 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 conducting clinical studies covered by the regulation. The EARLY TAVR study involved 538 investigators, of which none were full-time or part-time employees of the sponsor and 78 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: 78
- 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)(3) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the clinical study, patients in the CS cohort generally experienced worsening left heart health (as measured by LV longitudinal global strain, LV mass index, and LA volume index), functional status (as measured by NYHA function class and 6MWT distance), and health status (as measured by KCCQ, EQ-5D-5L, and SF-36), compared to patients in the TAVR cohort. The proportion of patients with healthy left heart function at 2 years was 48.1% in the TAVR cohort and 35.9% in the CS cohort. In addition, the proportions of patients that are alive with a favorable KCCQ overall summary score at 2 years was 86.6% and 68.0%, respectively.

The majority of patients in the CS cohort progressed from being asymptomatic to being symptomatic and required AVR at a median time from randomization of 332.5 days, with an estimated 26.2% of patients undergoing AVR within 6 months of randomization and 71.4% by 2 years, despite all patients being confirmed to be asymptomatic at screening, including over 90% by negative stress test. Post DAVR, patients experienced a rapid improvement in left heart health, functional status, and health status, which became comparable between the TAVR and DAVR patients at 2 years.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The results from the nonclinical laboratory (e.g., biocompatibility, hydrodynamic performance, durability, and structural integrity) and animal studies demonstrated that this device is suitable for long-term implant.

During a median follow-up of 3.8 years, the TAVR cohort was found to be superior to the CS cohort for the primary composite endpoint of all-cause death, all stroke, or unplanned cardiovascular hospitalization (26.8% vs. 45.3%). The superiority was driven primarily by unplanned cardiovascular hospitalization, specifically by DAVR procedures within 6 months post randomization, in the CS cohort. Although significant benefit in mortality was not observed in asymptomatic patients treated with TAVR prior to developing symptoms, the difference in the rate of unplanned cardiovascular hospitalization is an indicator of the deleterious effects and rapid symptomatic progression experienced by many of the control patients.

C. Benefit-Risk Determination

The probable benefits of early TAVR with the SAPIEN 3 and SAPIEN 3 Ultra THV system in asymptomatic patients with severe aortic stenosis include improved valve hemodynamic performance, prevention of a decline in functional and health statuses, prevention of symptoms of aortic stenosis, and a reduction in heart failure hospitalization.

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

1. Patient Perspectives

Patient perspectives considered during the review included patient reported outcomes as measured by KCCQ, EQ-5D-5L, and SF-36.

In conclusion, given the available information above, the data support that for asymptomatic patients with severe native aortic stenosis, the probable benefits of TAVR with the SAPIEN 3 and SAPIEN 3 Ultra THV system outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the SAPIEN 3 and SAPIEN 3 Ultra THV system for the replacement of native aortic valves in asymptomatic patients with severe aortic stenosis. FDA has determined this conclusion is also applicable to the SAPIEN 3 Ultra RESILIA THV system.

XIII. CDRH DECISION

CDRH issued an approval order on April 30, 2025. The final conditions of approval cited in the approval order are described below.

- 1. Continued Follow-up of “EARLY TAVR” 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 5 years post-procedure. The safety and effectiveness endpoints include all-cause death, all stroke, death or disabling stroke, hospitalization, new onset atrial fibrillation, NYHA Functional Class, health status as evaluated by KCCQ score, hemodynamic valve performance and other echocardiographic parameters, and aortic valve intervention.
- 2. Registry-Based Real-World Use Surveillance:** The surveillance will be carried out to assess the real-world performance of the Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA THV system and the clinical outcomes of the device in patient populations under-enrolled in the pivotal trial. It will involve all consecutive patients with asymptomatic severe aortic stenosis treated within the first 2 years following device approval or a total of 2,000 consecutively treated patients, whichever is greater, who are

entered into the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry (enrollment period). Data collection will continue for under-enrolled racial and ethnic groups until each group has enrolled a minimum number of patients as specified: Black/African American, 100; Asian, 100, American Indian/Alaskan Native, 50, Native Hawaiian/Pacific Islander, 50; and Hispanic or Latino ethnicity, 100. Data collection will also continue for under-enrolled patients deemed to be at intermediate or greater risk for open surgical therapy until a minimum of 300 patients have been enrolled. All patients will be followed through 5 years post-procedure (follow-up duration). The clinical data through one (1) year will be collected through the TVT Registry. The follow-up data (including all-cause mortality, all stroke, and aortic valve reintervention) from year 2 through year 5 post-procedure will be obtained through linking the TVT Registry data with the Centers for Medicare and Medicaid Services (CMS) claims database.

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. Généreux P, Piazza N, Alu MC, et al. Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research. *Eur Heart Jnl* 2021; 42: 1825-1857
3. Food and Drug Administration. FDA Guidance: Multiple Endpoints in Clinical Trials Guidance for Industry (January 2017). Retrieved from <https://www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf>
4. Westfall, K. Optimally weighted, fixed sequence, and gatekeeping multiple testing procedures. *J Stat Plan Inference* 2001; 99:25-40.