SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Aortic valve, prosthesis, percutaneously delivered
Device Trade Name:	Medtronic CoreValve Evolut R System Medtronic CoreValve Evolut PRO System
Device Procode:	NPT
Applicant Name and Address:	Medtronic CoreValve LLC 3576 Unocal Place Santa Rosa, CA 95403
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P130021/S058
Date of FDA Notice of Approval:	August 16, 2019

The original PMA of the Medtronic CoreValve System, P130021, was first approved on January 17, 2014. The device has since undergone two new design iterations: the Evolut R System was approved under P130021/S014 (for sizes 23, 26, and 29 mm) and P130021/S025 (for size 34 mm) on June 22, 2015, and October 26, 2016, respectively; and the Evolut PRO System was approved under P130021/S029 on March 20, 2017. The indication has also since been expanded in Panel Track PMA Supplements P130021/S002, P130021/S010, and P130021/S033 on June 12, 2014, March 30, 2015, and July 10, 2017, respectively, to include: (1) 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 comorbidities unmeasured by the STS risk calculator); and (2) patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic 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., STS predicted risk of operative mortality score ≥8% or at a ≥15% risk of mortality at 30 days).

The SSEDs to support the indication are available on the following FDA websites and are incorporated by reference herein:

- P130021: http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021b.pdf

- P130021/S002: http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021S002b.pdf
- P130021/S010: http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021S010B.pdf
- P130021/S033: https://www.accessdata.fda.gov/cdrh_docs/pdf13/p130021s033b.pdf

The current supplement was submitted to expand the indications for use of the Evolut R System and Evolut PRO 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 Medtronic CoreValve Evolut R System and Medtronic CoreValve Evolut PRO 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 CoreValve Evolut R system and the CoreValve Evolut PRO system are contraindicated in patients who cannot tolerate Nitinol (Titanium or Nickel), 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 Medtronic Evolut R System and Evolut PRO System labeling.

V. DEVICE DESCRIPTION

The Medtronic Evolut R and Evolut PRO Systems each consists of 3 components: the Transcatheter Aortic Valve (TAV), the Delivery Catheter System (DCS), and the Loading System (LS).

- **Medtronic Evolut R System**

  The Evolut R TAV (models EVOLUTR-23-US, EVOLUTR-26-US, EVOLUTR-29-US, and EVOLUTR-34-US), as shown in Figure 1, is a design iteration of the CoreValve TAV. It provides the optional capability of allowing for resheathing and/or complete recapture and redeployment during valve deployment. The Evolut R TAV is fully functional at approximately 2/3 partial deployment from the DCS. Once the TAV is fully deployed, it is not retrievable from the site of implantation.

Figure 1: Evolut R Transcatheter Aortic Valve

The Evolut R TAV can be delivered interchangeably using the EnVeo R DCS (models ENVEOR-US, ENVEOR-N-US, ENVPRO-14-US, and ENVPRO-16-US) or EnVeo PRO DCS (models ENVEOR-N-US and ENVPRO-16-US), which is a single use, intravascular, over-the-wire delivery catheter, as shown in Figure 2 and Figure 3, respectively. Both systems are designed to be compatible with commercially available 0.035″ intravascular wires and incorporate a protective deployment sheath that houses and deploys the prosthesis.

Figure 2: EnVeo R Delivery Catheter System

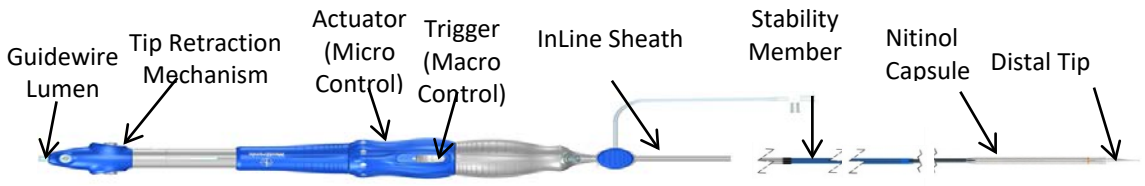
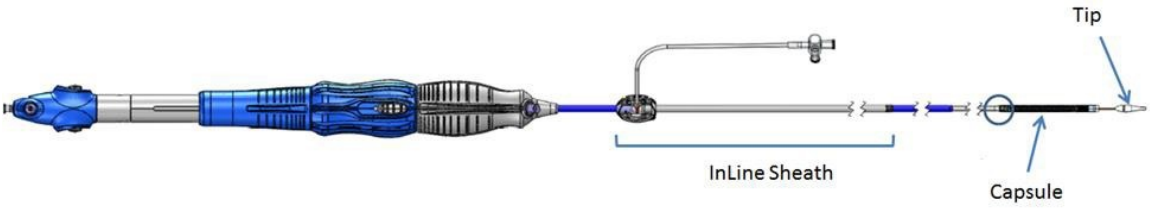


Figure 3: EnVeo PRO Delivery Catheter System



The Evolut R TAV can be loaded onto the delivery system using the EnVeo R LS (models LS-ENVEOR-23US, LS-ENVEOR-2629US, LS-ENVEOR-34US, LS-ENVPRO-14-US, and L-ENVPRO-16-US) or EnVeo PRO LS (models LS-MDT2-23-US, and LS-MDT2-2629-US, L-ENVPRO1623-US, and L-ENVPRO-16-US), as shown in Figure 4 and Figure 5, respectively.

Figure 4: EnVeo R Loading System

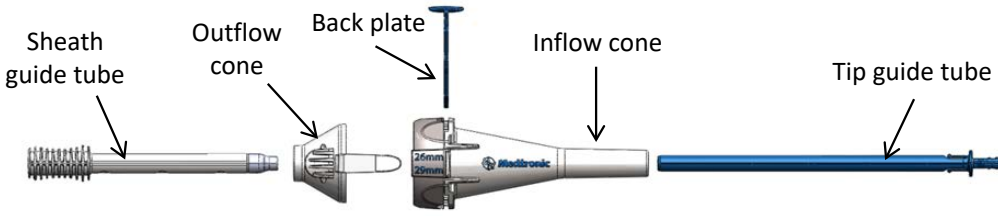


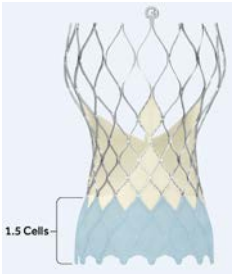
Figure 5: EnVeo PRO Loading System

1. Inflow ring
2. Inflow cone
3. Outflow cone
4. Back plate
5. Capsule Guide Tube
6. Tip guide tube

- **<u>Medtronic Evolut PRO System</u>**

  The Evolut PRO TAV, as shown in Figure 6, is a design iteration of the Evolut R TAV, with the addition of a porcine pericardial tissue wrap on the outside of the frame (outer wrap) that covers the inflow portion of the TAV to reduce paravalvular regurgitation.

Figure 6: Evolut PRO Transcatheter Aortic Valve



All three sizes of the Evolut PRO TAVs are deployed using the 20 Fr EnVeo R DCS or 16 Fr equivalent EnVeo PRO DCS.

The EnVeo R LS used with the Evolut PRO TAV is similar to that used with the Evolut R TAV, with minor design modifications to the inflow cone, the inflow ring, and the outflow cone. The Evolut PRO TAVs can also be used with the EnVeo PRO LS, similar to that used with the Evolut R TAVs.

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 expectations and lifestyle.

VII. MARKETING HISTORY

The Medtronic CoreValve Evolut R System and CoreValve Evolut PRO 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 Medtronic CoreValve Evolut R System and CoreValve Evolut PRO System:

- Death
- Myocardial infarction, cardiac arrest, cardiogenic shock, cardiac tamponade
- Coronary occlusion, obstruction, or vessel spasm (including acute coronary closure)
- Cardiovascular injury (including rupture, perforation, tissue erosion, or dissection of vessels, ascending aorta trauma, ventricle, myocardium, or valvular structures that may require intervention)
- Emergent surgical or transcatheter intervention (for example, coronary artery bypass, heart valve replacement, valve explant, percutaneous coronary intervention [PCI], balloon valvuloplasty)
- Prosthetic valve dysfunction (regurgitation or stenosis) due to fracture; bending (out-of-round configuration) of the valve frame; underexpansion of the valve frame; calcification; pannus; leaflet wear, tear, prolapse, or retraction; poor valve coaptation; suture breaks or disruption; leaks; mal-sizing (prosthesis-patient mismatch); malposition (either too high or too low)/malplacement
- Prosthetic valve migration/embolization
- Prosthetic valve endocarditis
- Prosthetic valve thrombosis
- Delivery catheter system malfunction resulting in the need for additional re-crossing of the aortic valve and prolonged procedural time
- Delivery catheter system component migration/embolization
- Stroke (ischemic or hemorrhagic), transient ischemic attack (TIA), or other neurological deficits
- Individual organ (for example, cardiac, respiratory, renal [including acute kidney failure]) or multi-organ insufficiency or failure

- Major or minor bleeding that may require transfusion or intervention (including life-threatening or disabling bleeding)
- Vascular access-related complications (for example, dissection, perforation, pain, bleeding, hematoma, pseudoaneurysm, irreversible nerve injury, compartment syndrome, arteriovenous fistula, stenosis)
- Mitral valve regurgitation or injury
- Conduction system disturbances (for example, atrioventricular node block, left-bundle branch block, asystole), which may require a permanent pacemaker
- Infection (including septicemia)
- Hypotension or hypertension
- Hemolysis
- Peripheral ischemia
- Bowel ischemia
- Abnormal lab values (including electrolyte imbalance)
- Allergic reaction to antiplatelet agents, contrast medium, or anesthesia
- Exposure to radiation through fluoroscopy and angiography
- Permanent disability

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 transcatheter aortic valve replacement (TAVR) with the CoreValve Evolut R System and CoreValve Evolut PRO System for patients with severe, native, calcific, aortic stenosis deemed by a heart team to be at low risk for open surgical therapy under IDE #G160022 (entitled the "Low Risk Trial"). Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were enrolled between March 25, 2016 and November 26, 2018. The database for this Panel Track PMA Supplement reflected data collected through November 30, 2018 and included 1468 randomized patients. There were 86 investigational sites in the US, Canada, Australia, New Zealand, Europe, and Japan.

The Low Risk Trial was a prospective, randomized (1:1), multi-center investigational study intended to determine whether TAVR is non-inferior to SAVR (with an absolute margin, δ, of 0.06) with respect to the primary endpoint. The randomization was stratified by investigational site and the need for revascularization. The sample size of the trial was

1200 patients. The trial employed Bayesian adaptive statistical methods to allow for a first "early win" analysis to be performed when 850 patients would have been followed for 12 months. At the first "early win" analysis, if the posterior probability, $Prob(H_{A,\delta=0.06}|\text{data})$ with H_A being defined as the alternative hypothesis, was to be greater than 0.972, non-inferiority would be declared at this time; otherwise, a second "early win" analysis would occur when 1200 patients would have reached 12 months follow-up. If non-inferiority was not to be reached, all 1200 patients would be followed to 24 months when a final analysis would occur. At the final analysis, the standard for trial success would again be $Prob(H_{A,\delta=0.06}|\text{data}) > 0.972$.

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.

Additional patients were enrolled in the trial after 1200 patients had been enrolled to complete the CT substudy and a cohort in Japan, resulting in a combined sample size of 1468 randomized patients at the time of the database lock.

Independent designees were utilized for interpretation and analysis of data for several aspects of the study, including: an independent Data Safety Monitoring Board (DSMB) with an independent statistician, a Clinical Events Committee (CEC) that was responsible for adjudicating adverse events, an echocardiography core laboratory, and a contract research organization that participated in source data verification. A computer tomography (CT) core laboratory was used for assessment of CT images acquired in the CT substudy.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the Low Risk Trial was limited to patients who met the following inclusion criteria:

   - Severe aortic stenosis, defined as follows:
     - For symptomatic patients:
       - Aortic valve area ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), OR mean gradient ≥40 mmHg, OR maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest.
     - For asymptomatic patients:
       - Very severe aortic stenosis with an aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), AND maximal aortic velocity ≥5.0 m/sec, or mean gradient ≥60 mmHg by transthoracic echocardiography at rest, OR
       - Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), AND a mean gradient ≥40 mmHg or maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest, AND an exercise tolerance test that demonstrates a limited exercise capacity, abnormal BP response, or arrhythmia, OR

    - Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), AND mean gradient ≥40 mmHg, or maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest, AND a left ventricular ejection fraction <50%.
- Patient is considered low risk for SAVR, where low risk is defined as predicted risk of mortality for SAVR <3% at 30 days per multidisciplinary local heart team assessment.
- The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.

Patients were not permitted to enroll in the Low Risk Trial if they met any of the following clinical or anatomical exclusion criteria:

- Any condition considered a contraindication for placement of a bioprosthetic valve (eg, subject is indicated for mechanical prosthetic valve).
- A known hypersensitivity or contraindication to any of the following that cannot be adequately pre-medicated:
    - aspirin or heparin (HIT/HITTS) and bivalirudin
    - ticlopidine and clopidogrel
    - Nitinol (titanium or nickel)
    - contrast media
- Blood dyscrasias as defined: leukopenia (WBC <1000 mm^3), thrombocytopenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy, or hypercoagulable states.
- Ongoing sepsis, including active endocarditis.
- Any percutaneous coronary or peripheral interventional procedure with a bare metal stent within 30 days prior to randomization, or drug eluting stent performed within 180 days prior to randomization.
- Multivessel coronary artery disease with a Syntax score >22 and/or unprotected left main coronary artery.
- Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 10 weeks of Heart Team assessment.
- Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.
- Recent (within 2 months of Heart Team assessment) cerebrovascular accident (CVA) or transient ischemic attack (TIA).
- Gastrointestinal (GI) bleeding that would preclude anticoagulation.
- Subject refuses a blood transfusion.
- Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits).
- Estimated life expectancy of less than 24 months due to associated non-cardiac co-morbid conditions.
- Other medical, social, or psychological conditions that in the opinion of the

investigator precludes the subject from appropriate consent or adherence to the protocol required follow-up exams.

- Currently participating in an investigational drug or another device trial (excluding registries).
- Evidence of an acute myocardial infarction ≤30 days before the trial procedure due to unstable coronary artery disease (WHO criteria).
- Need for emergency surgery for any reason.
- Subject is pregnant or breastfeeding.
- Subject is less than legal age of consent, legally incompetent, or otherwise vulnerable.
- Pre-existing prosthetic heart valve in any position.
- Severe mitral regurgitation amenable to surgical replacement or repair.
- Severe tricuspid regurgitation amenable to surgical replacement or repair.
- Moderate or severe mitral stenosis amenable to surgical replacement or repair.
- Hypertrophic obstructive cardiomyopathy with left ventricular outflow gradient.
- Bicuspid aortic valve verified by echocardiography, multiple detector computed tomography (MDCT), or magnetic resonance imaging (MRI).
- Prohibitive left ventricular outflow tract calcification.
- Sinus of Valsalva diameter unsuitable for placement of the self-expanding bioprosthesis.
- Aortic annulus diameter of <18 or >30 mm.
- Significant aortopathy requiring ascending aortic replacement.
- For transfemoral or transaxillary (subclavian) access:

  Access vessel mean diameter <5.0 mm for Evolut 23R, 26R, or 29R mm TAV, or access vessel mean diameter <5.5 mm for Evolut 34R mm or Evolut PRO TAV. However, for transaxillary (subclavian) access in patients with a patent LIMA, access vessel mean diameter <5.5mm for Evolut 23R, 26R, or 29R mm TAV, or access vessel mean diameter <6.0 mm for the Evolut 34R or Evolut PRO TAV.

2. Follow-Up Schedule

   All patients were scheduled for follow-up examinations at discharge, 30 days, 6 months, 1 year, 18 months, 2 years, and annually thereafter to a minimum of 10 years post-procedure, with the clinical assessments at 6, 8, and 9 years being conducted via telephone. Preoperative and post-operative assessments included physical assessment and patient interview, laboratory measurements, imaging tests, and health status/quality of life (QoL) questionnaire. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

Primary Endpoint:

The primary endpoint was all-cause mortality or disabling stroke rate at 24 months, with the following alternative hypothesis:

$$H_A: \pi_{TAVR} < \pi_{SAVR} + 0.06$$

where π_{TAVR} and π_{SAVR} denote binary rates of all-cause mortality or disabling stroke at 24 months for the TAVR (treatment) and SAVR (control) cohorts, respectively.

Secondary Endpoints:

The following ordered list of secondary endpoints, as shown in Table 1, were evaluated in a hierarchical testing scheme:

Table 1: Ordered List of Secondary Endpoints for Hierarchical Testing

Order	Secondary Endpoint	Alternative Hypothesis
#1	Transvalvular mean gradient at 12 months (non-inferiority)	$H_A: \mu_{TAVR} < \mu_{SAVR} + 5$
#2	Effective orifice area (EOA) at 12 months (non-inferiority)	$H_A: \mu_{TAVR} > \mu_{SAVR} - 0.1$
#3	Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score from baseline to 12 months (non-inferiority)	$H_A: \mu_{TAVR} > \mu_{SAVR} - 5$
#4	Change in New York Heart Association (NYHA) classification from baseline to 12 months (non-inferiority)	$H_A: \mu_{TAVR} > \mu_{SAVR} - 0.375$
#5	Transvalvular mean gradient at 12 months (superiority)	$H_A: \mu_{TAVR} < \mu_{SAVR}$
#6	EOA at 12 months (superiority)	$H_A: \mu_{TAVR} > \mu_{SAVR}$
#7	Change in KCCQ overall score from baseline to 30 days (superiority)	$H_A: \mu_{TAVR} > \mu_{SAVR}$

B. Accountability of PMA Cohort

At the time of database lock, a total of 1468 patients were randomized in this study, including 734 TAVR patients and 734 SAVR patients.

There were four different analysis populations defined in the statistical analysis plan of the study: intention-to-treat (ITT), as treated (AT), implanted, and per protocol

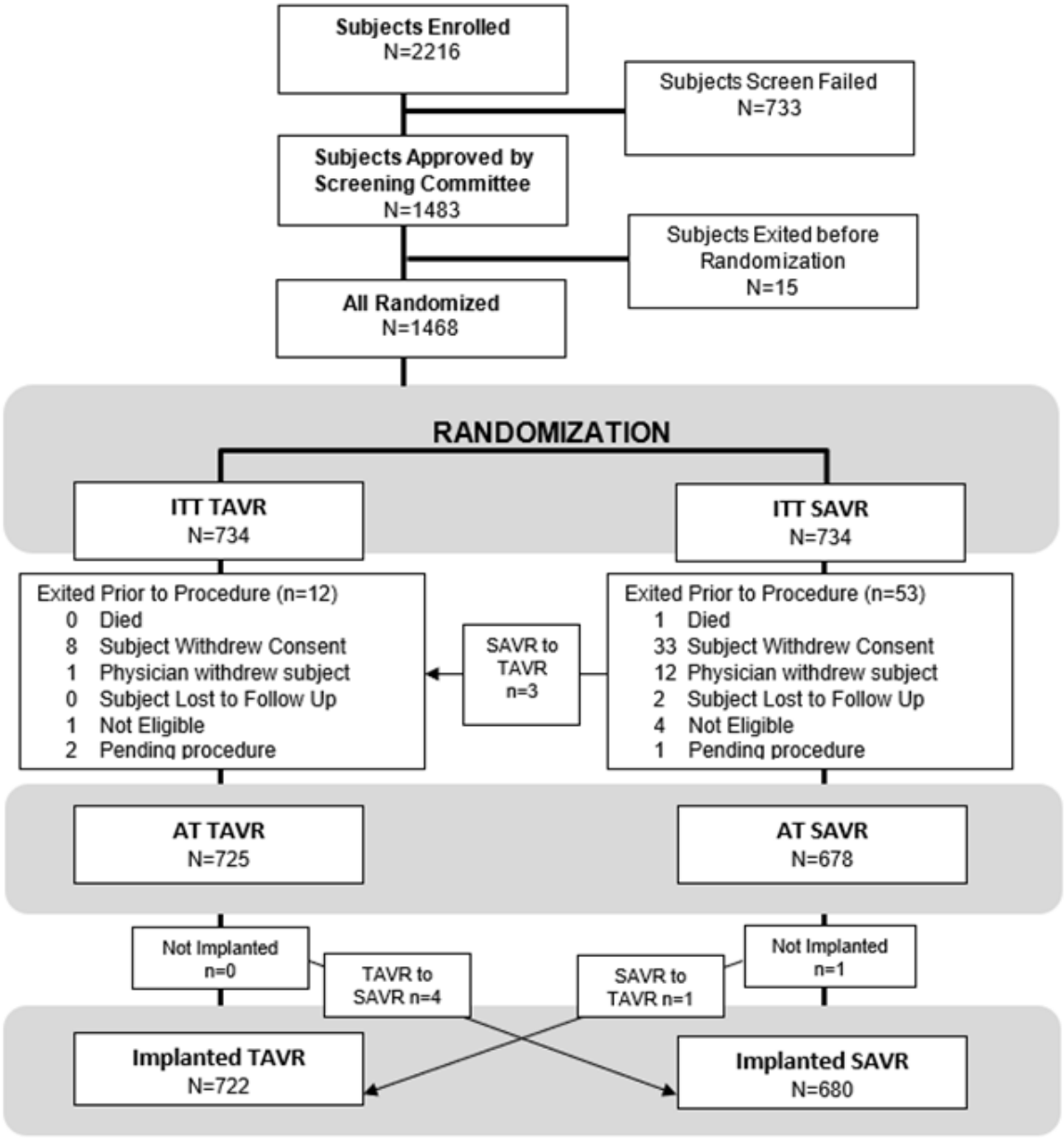
(PP), as summarized in Table 2 and Figure 7. The primary analysis was the AT analysis.

Table 2: Analysis Populations

Analysis Population	Definition	Number of Patients	
		SAVR	TAVR
Intention-to-treat (ITT)	All randomized patients	734	734
As treated (AT)	All ITT patients with an attempted implant procedure*	725	678
Implanted	All AT patients who were actually implanted with a valve	722	680
Per protocol (PP)	Based on the International Council for Harmonisation (ICH) E9 Statistical Principals: – All implanted patients who were implanted according to their randomization; and – Patients without early exit (e.g., lost to follow-up) before 24 months (730 days), except those experiencing the primary endpoint (death or disabling stroke) prior to the early exit; and – Patients without crossover to a different type of procedure from their first attempted procedure type before their 24-month visits; and – Patients must satisfy all inclusion/exclusion criteria.	702	647

*Attempted implant procedure was defined as when the subject was brought into the procedure room and any of the following had occurred: anesthesia administered, vascular line placed, transesophageal echocardiography probe placed, or any monitoring line placed. Patients were analyzed according to their first attempted procedure (TAVR or SAVR).

Figure 7: Population Flowchart



Of the 722 patients in the implanted TAVR cohort, 534 patients were implanted with the Evolut R TAV, 162 patients with the Evolut PRO TAV, and 26 patients with the CoreValve 31 mm TAV.

The overall follow-up compliance of the trial is summarized in Table 3. The compliance rates were similar for TAVR and SAVR patients at each visit through 24 months.

Table 3: Overall Study Compliance (ITT Population)

Visit Interval	Number Expected*	Visit Completed	Study Exits					Pending Next Visit
			Not Eligible	Died	Withdrew†	Lost to Follow Up	Other	
TAVR								
Randomized	734	100.0%	1	0	9	0	0	2
Procedure	722	100.0%	0	3	0	0	0	0
Discharge	719	100.0%	0	0	0	0	0	0
1-Month	719	99.9%	0	6	2	1	0	2
6-Month	708	98.7%	0	6	3	0	0	81
12-Month	618	98.5%	0	2	5	0	0	222
18-Month	389	96.4%	0	4	0	1	0	190
24-Month	194	96.4%	0	0	0	0	0	190
SAVR								
Randomized	734	100.0%	4	1	45	2	0	1
Procedure	681	100.0%	0	6	2	0	0	0
Discharge	673	100.0%	0	2	3	0	0	0
1-Month	668	99.1%	0	5	10	0	0	2
6-Month	651	96.3%	0	6	9	1	0	95
12-Month	540	96.9%	0	2	5	2	0	208
18-Month	323	94.1%	0	0	1	0	0	160
24-Month	162	96.3%	0	1	2	0	0	156

*Number of expected visits in an interval = (# of expected visits in the previous interval - # not eligible - # died - # withdrew - # lost to follow up - # other - # pending).
†Withdrew includes subjects who withdrew consent and who were withdrawn from study by physician.

C. Study Population Demographics and Baseline Parameters

The demographics and baseline characteristics of the study population are typical for a TAVR study performed in the U.S., as summarized in Table 4. The treatment cohorts were generally well balanced with respect to age, gender, baseline NYHA classification, and STS risk score.

Table 4: Patient Demographics and Baseline Characteristics (AT Population)

Demographics and Baseline Characteristics	Summary Statistics*		
	TAVR	SAVR	Difference (TAVR – SAVR) (95% BCI)
Age (years)	74.1 ± 5.8 (725)	73.6 ± 5.9 (678)	(-0.17, 1.07)
Gender female (%)	36.0% (261/725)	33.8% (229/678)	(-2.77%, 7.18%)
NYHA class			
I	10.5% (76/725)	9.3% (63/678)	(-1.95%, 4.30%)
II	64.4% (467/725)	62.2% (422/678)	(-2.85%, 7.21%)
III	25.0% (181/725)	28.0% (190/678)	(-7.64%, 1.57%)
IV	0.1% (1/725)	0.4% (3/678)	(-1.07%, 0.34%)
STS score, %	1.9 ± 0.7 (725)	1.9 ± 0.7 (678)	(-0.03, 0.11)
Peripheral arterial disease	7.5% (54/718)	8.3% (56/677)	(-3.62%, 2.09%)
Previous myocardial infarction	6.6% (48/725)	4.9% (33/678)	(-0.70%, 4.20%)
Previous reintervention			
Coronary artery bypass Surgery	2.5% (18/725)	2.1% (14/678)	(-1.20%, 2.02%)
Percutaneous coronary Intervention (PCI)	14.2% (103/725)	12.8% (87/678)	(-2.21%, 4.94%)
Cerebrovascular disease	10.2% (74/725)	11.8% (80/678)	(-4.90%, 1.67%)
Immunosuppressive therapy	2.1% (15/725)	0.9% (6/678)	(-0.11%, 2.53%)
Chronic lung disease/COPD	15.0% (104/695)	18.0% (117/649)	(-7.04%, 0.90%)
Diabetes	31.4% (228/725)	30.5% (207/678)	(-3.91%, 5.73%)
Creatinine level > 2 mg/dl	0.4% (3/725)	0.1% (1/678)	(-0.41%, 0.98%)
Atrial fibrillation/atrial flutter	15.4% (111/722)	14.5% (98/676)	(-2.86%, 4.60%)
Pre-existing permanent pacemaker or defibrillator	3.2% (23/725)	3.8% (26/677)	(-2.66%, 1.28%)
Hypertension	84.8% (614/724)	82.6% (559/677)	(-1.63%, 6.11%)
Dialysis	0.0% (0/725)	0.1% (1/678)	(-0.72%, 0.31%)
Echocardiographic findings - Implanted Population			
Aortic valve area (cm^2)	0.8 ± 0.2 (716)	0.8 ± 0.2 (673)	(-0.02, 0.02)
Mean gradient (mmHg)	47.0 ± 12.1 (724)	46.6 ± 12.2 (678)	(-0.87, 1.69)

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

D. Safety and Effectiveness Results

At the time of the first "early win" analysis, 168 patients had been followed for 24 months in the original dataset. Subsequently, a supplemental analysis was performed on an expanded dataset during the review of the PMA application, which included

additional follow-up data collected through May 3, 2019 when 410 patients had been followed for 24 months. The data presented in this section reflect the results of the supplemental analysis unless noted otherwise. Specifically, all hypothesis testing was conducted on the original dataset.

1. Primary Endpoint:

The first "early win" assessment of the primary endpoint of all-cause mortality or disabling stroke rate at 24 months included all patients in the AT population (N=1403). The median of the posterior distribution for the primary endpoint event rate was 5.3% for the TAVR cohort and 6.7% for the SAVR cohort, with a median of the posterior distribution of the difference in the primary endpoint event rate of -1.4% (TAVR-SAVR) and a 95% Bayesian credible interval (BCI) of (-4.9%, 2.1%), as summarized in Table 5. The posterior probability of non-inferiority with a margin of 6% was >0.999, which is greater than the pre-specified threshold of 0.972, thus the primary endpoint non-inferiority could be concluded.

Similarly, the supplemental analysis showed that the median of the posterior distribution for the primary endpoint event rate was 4.4% for the TAVR cohort and 6.2% for the SAVR cohort, with a median of the posterior distribution of the difference in the primary event rate of -1.8% (TAVR – SAVR) and a 95% BCI of (-4.6%, 1.0%), as summarized in Table 5. Hypothesis testing was not repeated on the expanded dataset because it was not prespecified; the supplemental analysis for the posterior probability of non-inferiority with a margin of 6% is shown for context.

Table 5: All-Cause Mortality or Disabling Stroke at 24 Months - AT Population

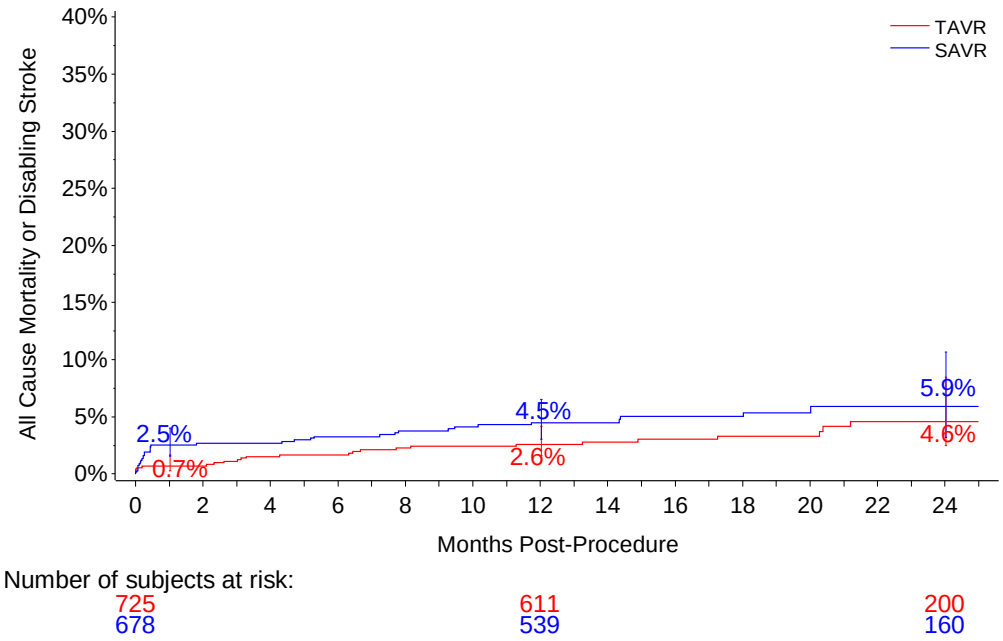
	"Early Win" Analysis*		**Supplemental Analysis†**	
	TAVR (N=725)	**SAVR (N=678)**	**TAVR (N=725)**	**SAVR (N=678)**
Posterior median (95% BCI)	5.3% (3.3%, 8.0%)	6.7% (4.4%, 9.6%)	4.4% (2.9%, 6.4%)	6.2% (4.3%, 8.6%)
Difference (TAVR-SAVR) posterior median (95% BCI)	-1.4% (-4.9%, 2.1%)		-1.8% (-4.6%, 1.0%)	
Primary objective – Non-inferiority				
Posterior probability $P(H_{A,\delta=0.06}\|\text{data})$	> 0.999		> 0.999	
Posterior threshold for non-inferiority	0.972			
Non-inferiority test	Passed			

*Conducted on the original dataset

†Conducted on the expanded dataset

The Kaplan-Meier (K-M) curve of all-cause mortality or disabling stroke is shown in Figure 8.

Figure 8: All-Cause Mortality or Disabling Stroke through 24 Months (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

Hypothesis testing was performed hierarchically on pre-specified secondary endpoints based on the original dataset, as shown in Table 6. TAVR was found to be non-inferior to SAVR within the pre-specified non-inferiority margins in terms of mean gradient and effective orifice area (EOA) at 12 months, the NYHA functional classification change from baseline to 12 months, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score change from baseline to 12 months. TAVR was found to be superior to SAVR with respect to mean gradient and EOA at 12 months and the KCCQ score change from baseline to 30 days (posterior probability > 0.999 for all).

Table 6: Secondary Endpoints Hierarchical Testing

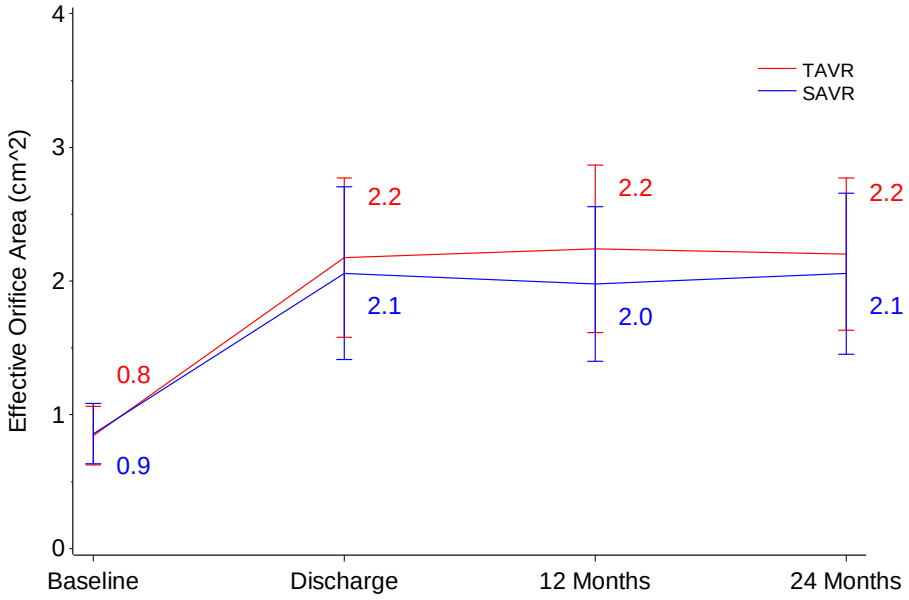
Secondary Endpoint	TAVR Mean±SD (N)	SAVR Mean±SD (N)	Difference (TAVR – SAVR) (90% BCI)	Posterior Probability Prob (H_A | data)	Threshold	Test Result
Non-inferiority testing						
#1 Mean gradient at 12 months	8.6 ± 3.7 (409)	11.2 ± 4.9 (339)	-2.6 (-3.1, -2.1)	>0.999	0.95	Passed
#2 EOA at 12 months	2.3 ± 0.7 (341)	2.0 ± 0.6 (293)	0.3 (0.2, 0.4)	>0.999	0.95	Passed
#3 NYHA change (baseline – 12 months)	0.9 ± 0.7 (428)	1.0 ± 0.7 (342)	-0.1 (-0.2, 0.0)	>0.999	0.95	Passed
#3 KCCQ overall score change (12 months – baseline)	22.2 ± 20.3 (428)	20.9 ± 21.0 (347)	1.3 (-1.2, 3.8)	>0.999	0.95	Passed
Secondary Endpoint	**TAVR Mean±SD (N)**	**SAVR Mean±SD (N)**	**Difference (TAVR – SAVR) (95% BCI)**	**Posterior Probability Prob (H | data)**	**Threshold**	**Test Result**
Superiority testing						
#4 Mean gradient at 12 months	8.6 ± 3.7 (409)	11.2 ± 4.9 (339)	-2.6 (-3.2, -2.0)	>0.999	0.975	Passed
#5 EOA at 12 months	2.3 ± 0.7 (341)	2.0 ± 0.6 (293)	0.3 (0.2, 0.4)	>0.999	0.975	Passed
#6 KCCQ overall score change (30 day – baseline)	20.0 ± 21.1 (713)	9.1 ± 22.3 (636)	10.9 (8.6, 13.2)	>0.999	0.975	Passed

Note: The Implanted population was used for the mean gradient and EOA, and the AT population was used for the rest. All testing was conducted on the original dataset.

Valve Performance

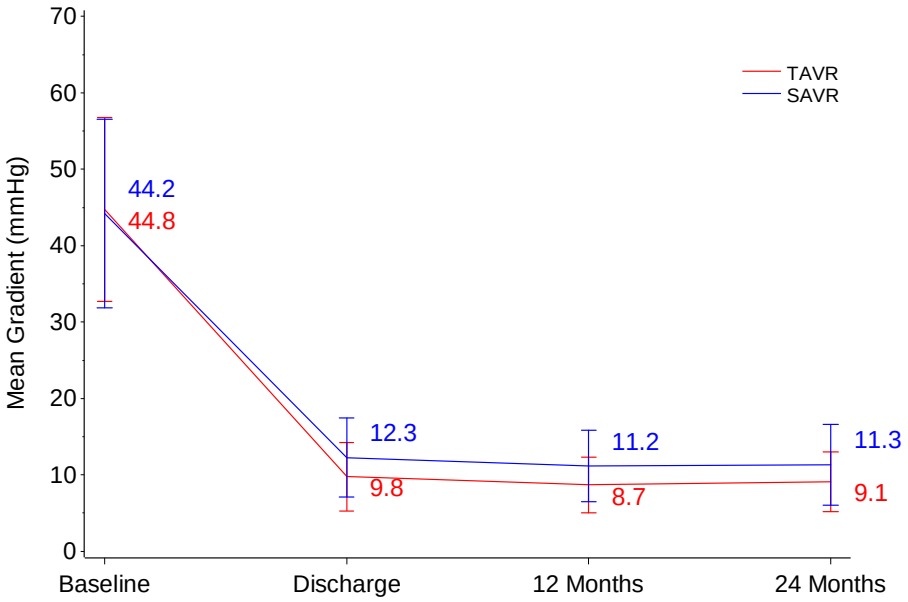
The EOA, mean aortic gradient, total aortic regurgitation (AR), and paravalvular regurgitation values obtained over time for the TAVR and SAVR patients are shown in Figure 9 through Figure 12, respectively. The increase in EOA and decrease in gradient were sustained through 24 months in both cohorts. In the TAVR cohort, the proportion of patients with total AR ≥ moderate was 4.6% at 12 months and 5.6% at 24 months, while in the SAVR cohort, the corresponding proportion was 1.4% at 12 months and 2.1% at 24 months. The proportion of patients with paravalvular regurgitation ≥ moderate was 4.0% at 12 months and 4.1% at 24 months in the TAVR cohort, as compared to 0.8% at 12 months and 0.7% at 24 months in the SAVR cohort.

Figure 9: Effective Orifice Area through 24 Months (Implanted Population)



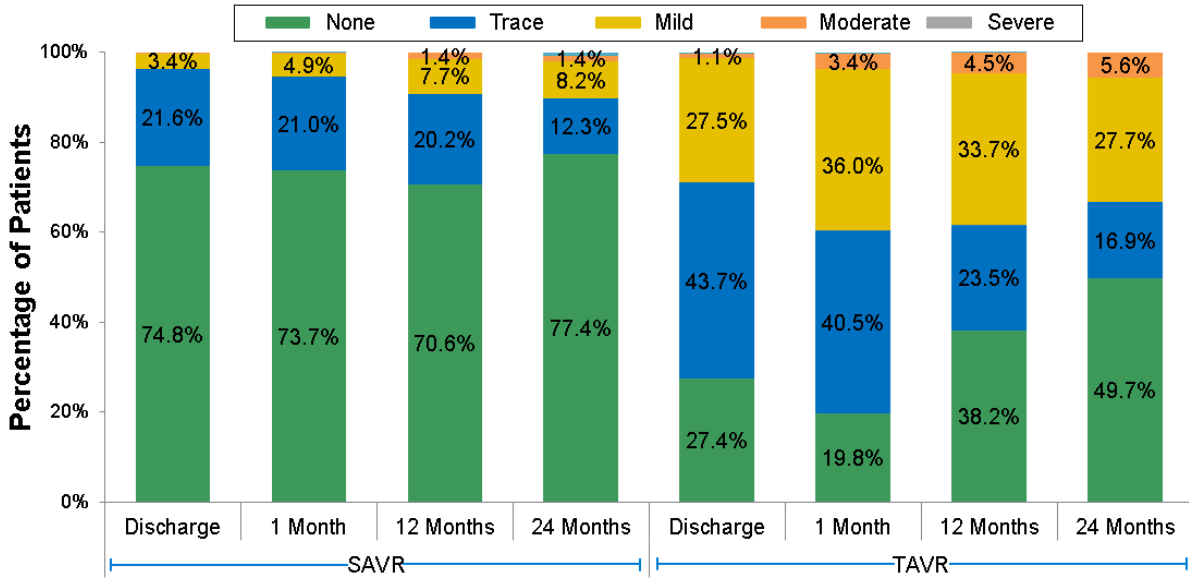
Note: Line plot with mean and standard deviation.

Figure 10: Mean Aortic Gradient through 24 Months (Implanted Population)



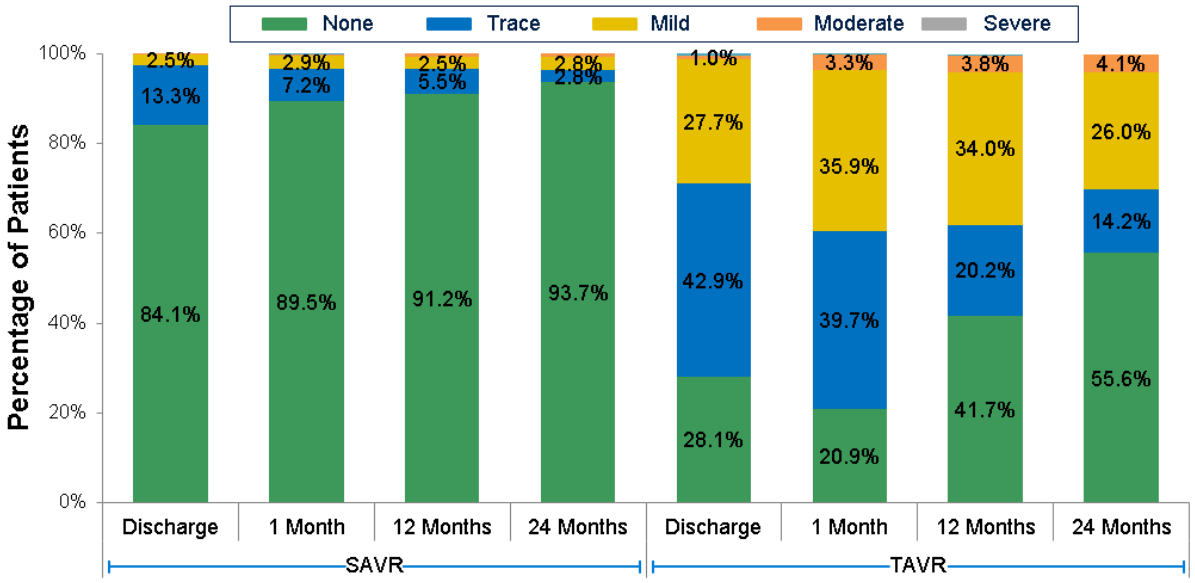
Note: Line plot with mean and standard deviation.

Figure 11: Total Aortic Regurgitation (Implanted Population)



Note: Values < 1.0% are not labeled.

Figure 12: Paravalvular Aortic Regurgitation by Visit (Implanted Population)

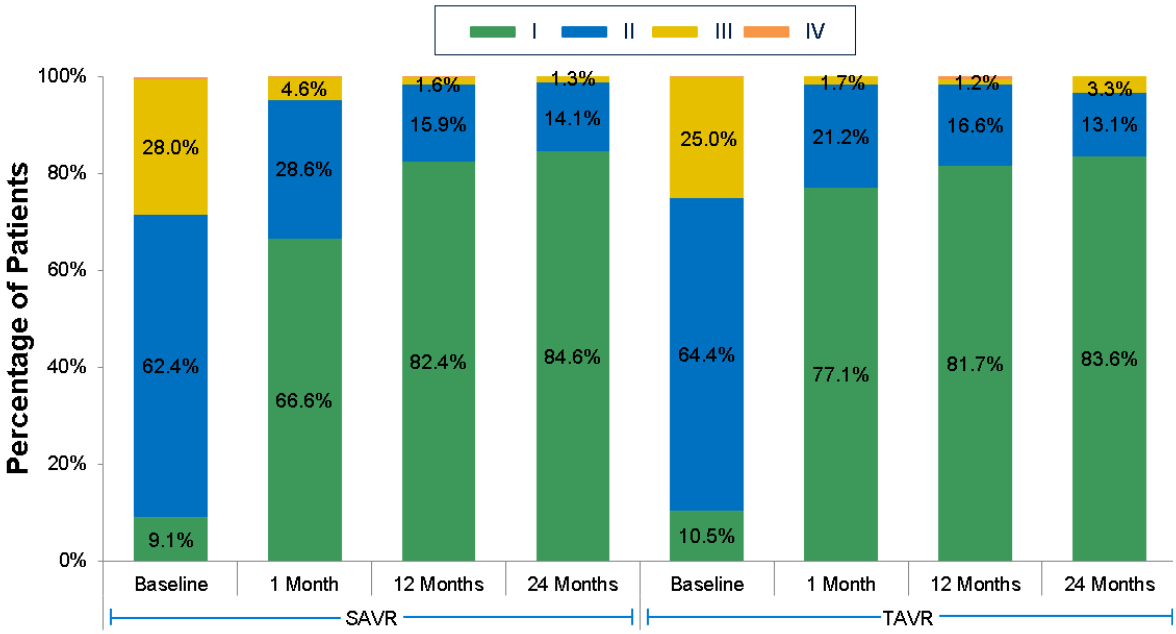


Note: Values < 1.0% are not labeled.

NYHA Functional Class

The NYHA classifications by visit are presented in Figure 13. At baseline, 25.1% of TAVR patients and 28.4% of SAVR patients were in NYHA III/IV. At 24 months, this percentage decreased to 3.3% in TAVR patients and 1.3% in SAVR patients.

Figure 13: NYHA Classification by Visit (AT Population)



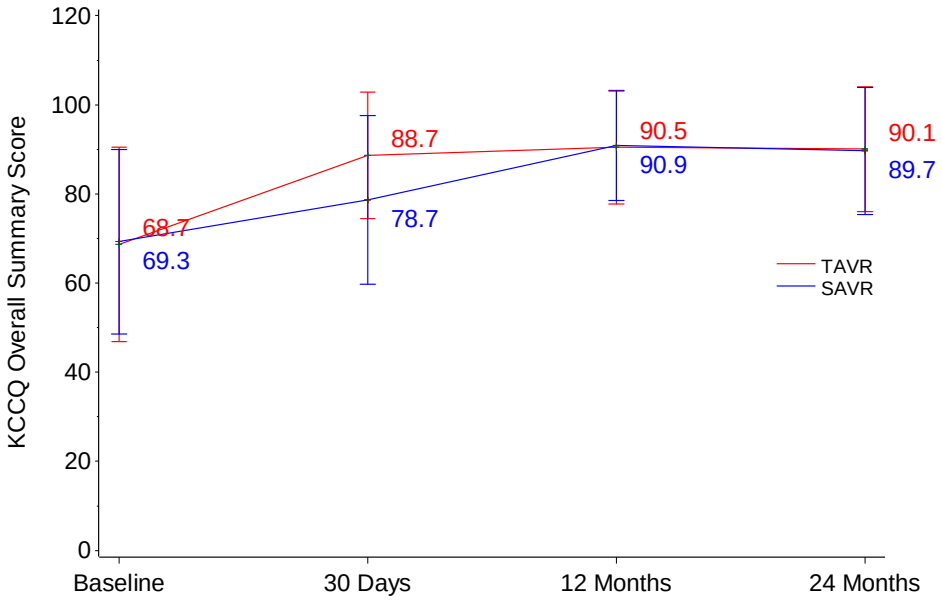
Note: Values < 1.0% are not labeled.

QoL

KCCQ

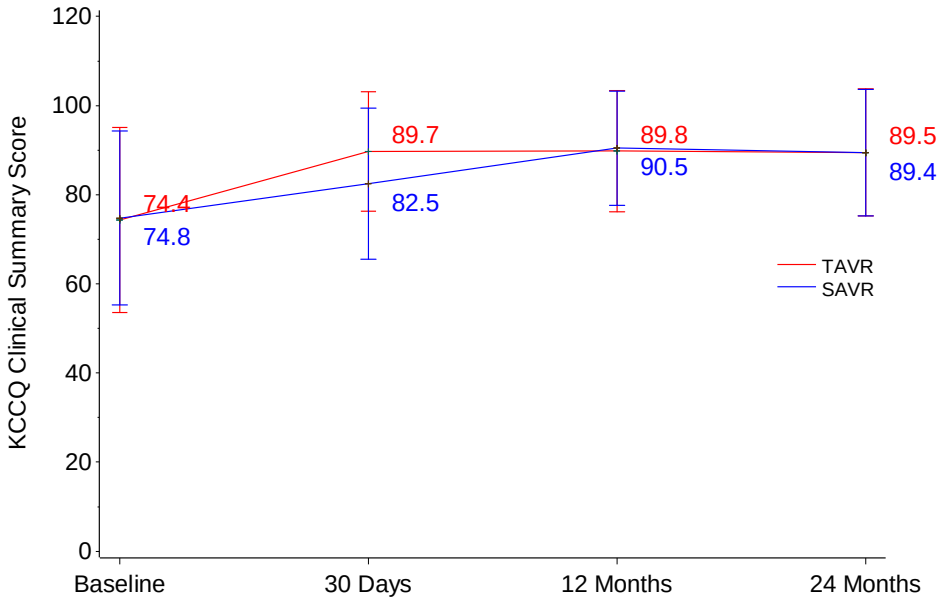
The KCCQ overall and clinical summary scores for the two treatment cohorts are shown in Figure 14 and Figure 15, respectively. In TAVR patients, the mean KCCQ overall summary score increased from 68.7 at baseline to 90.5 at 12 months and 90.1 at 24 months, and the mean KCCQ clinical summary score increased from 74.4 at baseline to 89.8 at 12 months and 89.5 at 24 months. Similar trends were observed in SAVR patients.

Figure 14: KCCQ Overall Summary Score (AT Population)



Note: Line plot with mean and standard deviation.

Figure 15: KCCQ Clinical Summary Score (AT Population)

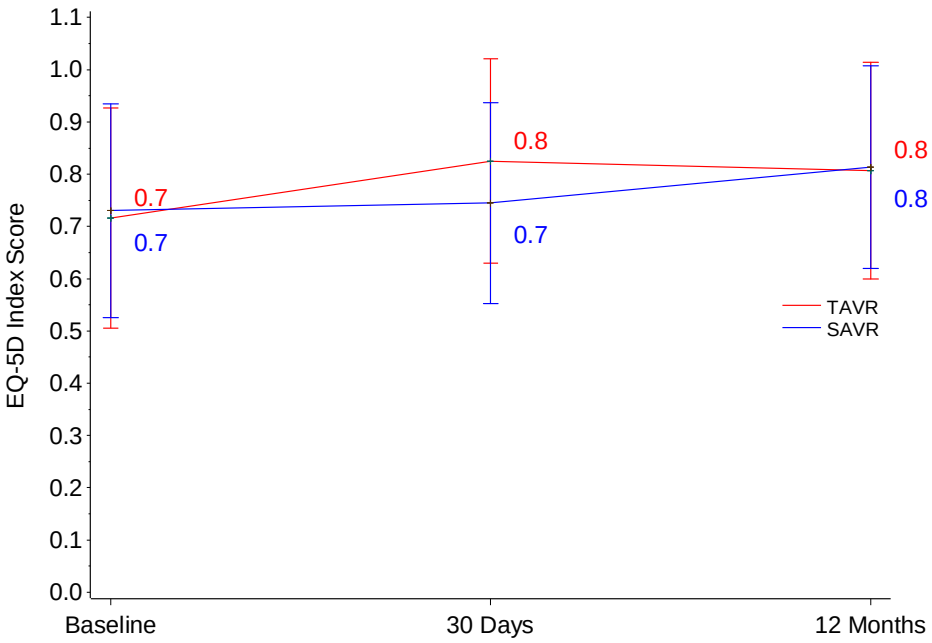


Note: Line plot with mean and standard deviation.

EuroQoL (EQ-5D)

The EQ-5D index scores for the two treatment cohorts are shown in Figure 16. The mean score was 0.7 at baseline, 0.8 at 30 days, and 0.8 at 12 months in TAVR patients, as compared to 0.7 at baseline, 0.7 at 30 days, and 0.8 at 12 months in SAVR patients.

Figure 16: EQ-5D Index Score (AT Population)



Note: Line plot with mean and standard deviation.

3. Adverse Events

The key adverse events that occurred in the trial through 24 months are presented in Table 7.

Table 7: Adverse Events through 24 Months (AT Population)

Events	Kaplan-Meier Rate *					
	0-30 Days		0-12 Months		0-24 Months	
	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
All-cause mortality or disabling stroke	0.7% (5, 6)	2.5% (17, 20)	2.6% (18, 21)	4.5% (29, 34)	4.6% (24, 28)	5.9% (33, 39)
All-cause mortality	0.4% (3, 3)	1.2% (8, 8)	2.2% (15, 15)	2.8% (18, 18)	4.0% (20, 20)	3.6% (21, 21)
Cardiovascular	0.4% (3, 3)	1.2% (8, 8)	1.6% (11, 11)	2.5% (16, 16)	2.7% (14, 14)	2.8% (17, 17)

Events	Kaplan-Meier Rate *					
	0-30 Days		0-12 Months		0-24 Months	
	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
Non-cardiovascular	0.0% (0, 0)	0.0% (0, 0)	0.6% (4, 4)	0.3% (2, 2)	1.3% (6, 6)	0.8% (4, 4)
Reintervention	0.3% (2, 2)	0.3% (2 2)	0.6% (4, 4)	0.5% (3, 3)	0.8% (5, 5)	1.3% (5, 5)
All stroke	3.5% (25, 25)	3.3% (22, 23)	4.3% (31, 33)	4.4% (29, 31)	6.4% (37, 39)	6.4% (33, 35)
Disabling stroke	0.4% (3, 3)	1.6% (11, 12)	0.8% (6, 6)	2.3% (15, 16)	1.5% (8, 8)	3.1% (17, 18)
Non-disabling stroke	3.0% (22, 22)	1.6% (11, 11)	3.5% (25, 27)	2.2% (15, 15)	4.9% (29, 31)	3.4% (17, 17)
Life threatening/disabling bleeding	2.3% (17, 17)	7.5% (51, 51)	3.5% (25, 25)	8.7% (58, 59)	4.1% (28, 28)	8.7% (58, 59)
Major vascular complication	3.7% (27, 27)	3.1% (21, 21)	3.7% (27, 27)	3.4% (23, 23)	4.2% (28, 28)	3.7% (24, 24)
Acute kidney injury - Stage 3	0.4% (3, 3)	1.8% (12, 12)	0.4% (3, 3)	1.8% (12, 12)	0.4% (3, 3)	1.8% (12, 12)
Myocardial infarction	0.8% (6, 6)	1.3% (9, 9)	1.8% (13, 15)	1.6% (11, 12)	2.0% (14, 16)	1.6% (11, 12)
Aortic valve hospitalization†	1.1% (8, 8)	2.4% (16, 17)	3.3% (23, 29)	6.2% (40, 44)	5.0% (30, 39)	7.5% (44, 53)
New permanent pacemaker implantation‡	17.3% (125, 125)	6.1% (41, 41)	19.1% (138, 138)	6.7% (45, 45)	22.7% (150, 150)	7.6% (48, 48)

*Kaplan-Meier rate (# patients, # events).
†Not adjudicated by CEC.
‡Patients with pacemaker or ICD at baseline were not counted as new events. Not adjudicated by CEC.

The patient prosthesis mismatch adjudicated by the core laboratory is summarized in Table 8.

Table 8: Patient Prosthesis Mismatch (Implanted Population)

Severity†	Summary Statistics*					
	30 Days		12 Months		24 Months	
	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
Severe	1.1% (7/610)	4.4% (24/545)	1.8% (9/489)	6.8% (30/438)	1.3% (2/154)	2.5% (3/120)
Moderate	10.0% (61/610)	16.0% (87/545)	5.5% (27/489)	16.7% (73/438)	7.1% (11/154)	14.2% (17/120)

Severity[†]	Summary Statistics[*]					
	30 Days		12 Months		24 Months	
	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
None	88.9% (542/610)	79.6% (434/545)	92.6% (453/489)	76.5% (335/438)	91.6% (141/154)	83.3% (100/120)

[*]Observed rate - % (no./total no.)

[†]Severe: (Body mass index [BMI] < 30 and effective orifice area index [EOAI] < 0.65) OR (BMI ≥ 30 and EOAI < 0.60); moderate: (BMI < 30 and 0.65 ≤ EOAI ≤ 0.85) OR (BMI ≥ 30 and 0.60 ≤ EOAI ≤ 0.70); none: (BMI < 30 and EOAI > 0.85) OR (BMI ≥ 30 and EOAI > 0.70)

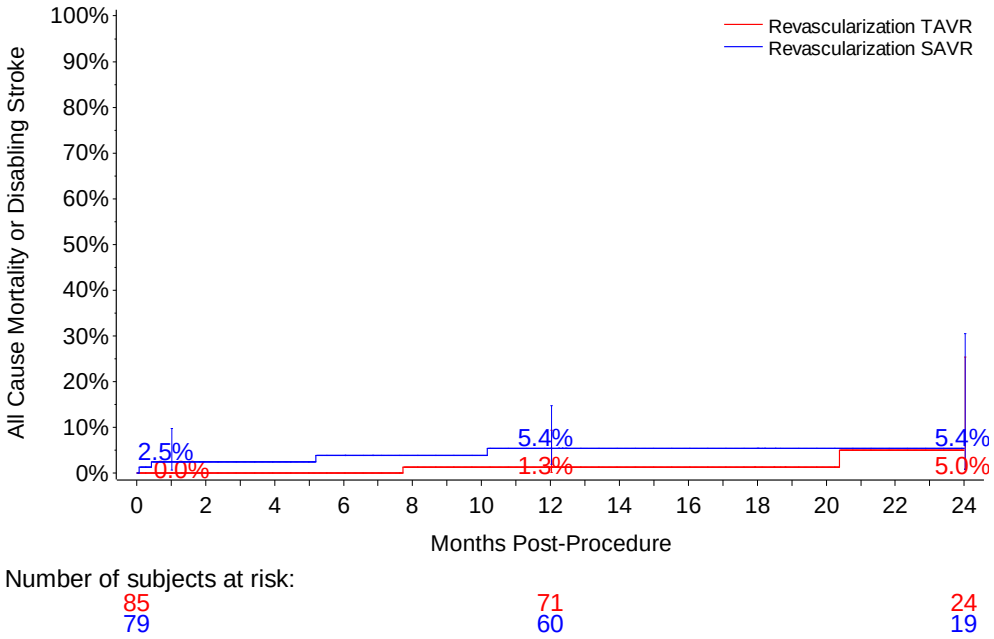
4. Subgroup Analyses

The protocol specified subgroup analyses of the primary endpoint of all-cause mortality or disabling stroke at 24 months by randomization designation (TAVR vs. SAVR) for patients with and without revascularization and for patients of different genders.

All-Cause Mortality or Disabling Stroke Stratified by Need for Revascularization:

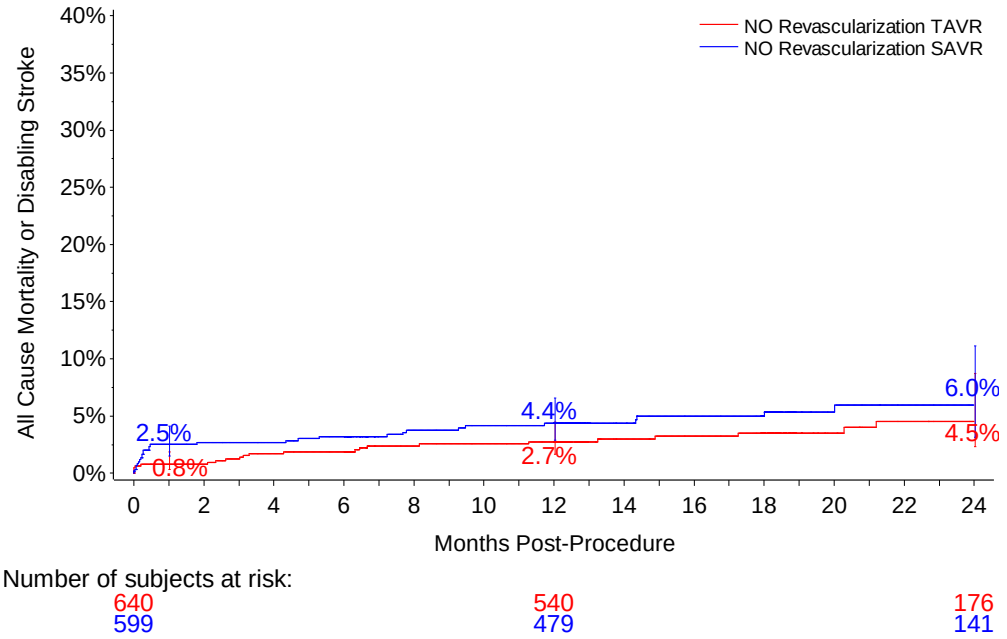
The K-M curves of all-cause mortality or disabling stroke are shown in Figures 17 and 18 for patients with and without the need for concomitant revascularization, respectively.

Figure 17: All-Cause Mortality or Disabling Stroke for Patients with Need for Revascularization – 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. The trial was not powered to assess the difference between the two subgroups.

Figure 18: All-Cause Mortality or Disabling Stroke for Patients without Need for Revascularization – AT Population

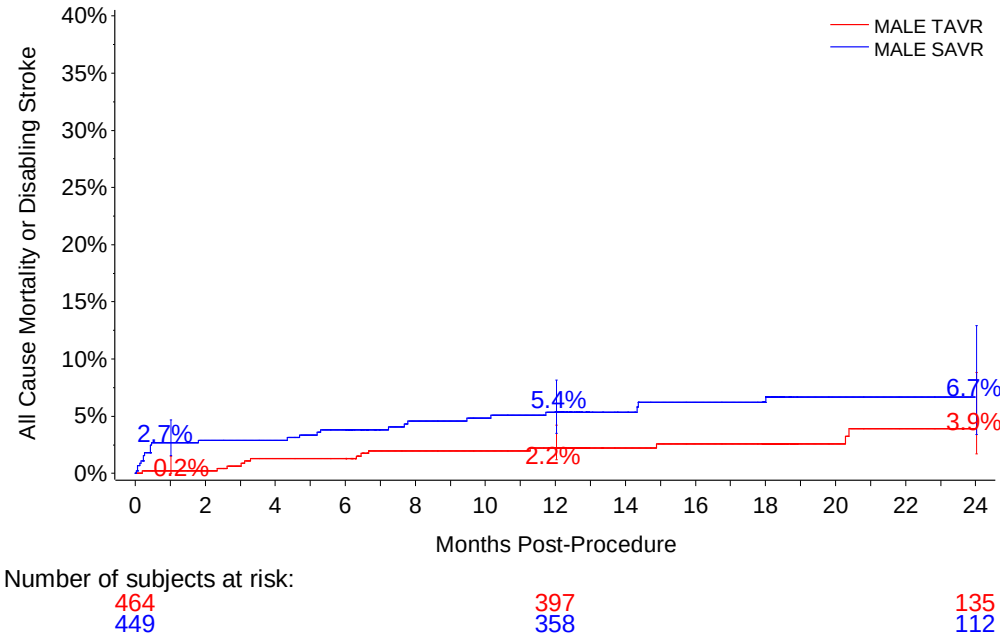


Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion. The trial was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

All-Cause Mortality or Disabling Stroke Stratified by Gender:

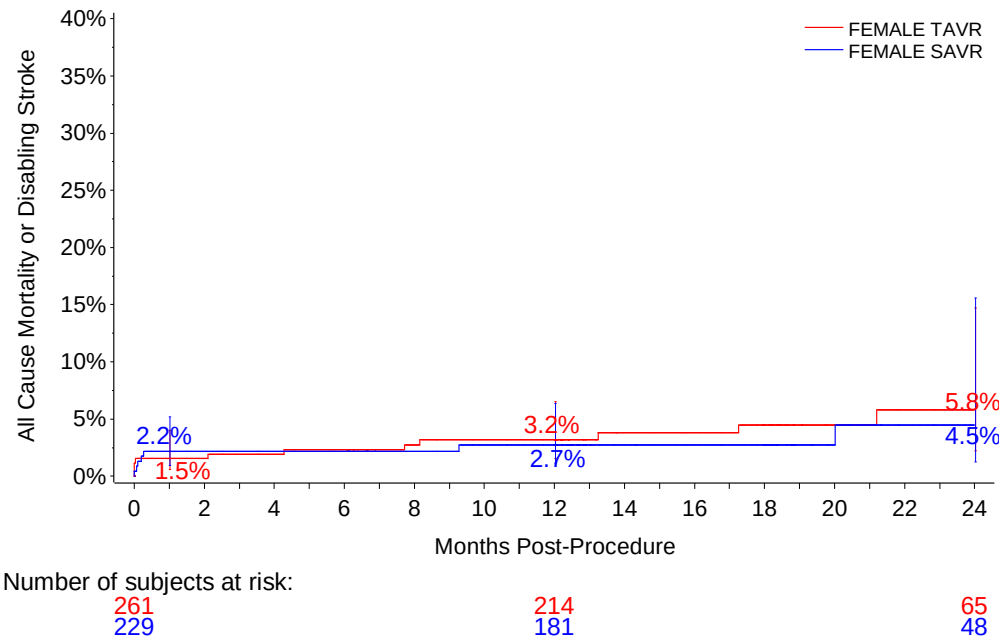
The K-M curves of all-cause mortality or disabling stroke are shown in Figures 19 and 20, for the male and female patients, respectively.

Figure 19: All-Cause Mortality or Disabling Stroke for Male Patients - 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. The trial was not powered to assess the difference between the two subgroups.

Figure 20: All-Cause Mortality or Disabling Stroke for Female Patients - 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. The trial was not powered to assess the difference between the two subgroups.

5. Other Study Observations

Procedure Data

The procedure data of the TAVR and SAVR cohorts are summarized in Table 9 and Table 10, respectively.

Table 9: TAVR Procedure Data (AT Population)

Procedure Data	Summary Statistics* (N=725)
Number of index procedures	724
Total delivery catheter in the body time (min)	17.4 ± 19.4
Type of anesthesia	
General	56.9% (412/724)
Local	43.1% (312/724)
Access site	
Iliofemoral	99.0% (717/724)

Procedure Data	Summary Statistics* (N=725)
Non-iliofemoral	1.0% (7/724)
Valve size	
23 mm	1.2% (9/721)
26 mm	19.6% (141/721)
29 mm	42.7% (308/721)
31 mm	3.6% (26/721)
34 mm	32.9% (237/721)
Total time in catheterization laboratory or operating room (min)	148.2 ± 55.1
Embolic protection device used	1.2% (9/722)
Pre-TAVR balloon valvuloplasty performed	34.9% (253/724)
Post-TAVR balloon valvuloplasty performed	31.3% (226/723)
Concomitant procedure (percutaneous coronary intervention; PCI)	6.9% (50/724)
Length of index hospitalization (days)	2.6 ± 2.1

*Continuous measures - Mean ± SD; categorical measures - % (no./total no.). Data included subjects with the index procedure defined as the first procedure in which the delivery catheter was introduced. If a patient had two implant procedures, the index procedure was used.

Table 10: SAVR Procedure Data (AT Population)

Procedure Data	Summary Statistics*
	SAVR (N=678)
Procedure aborted†	0.4% (3/678)
Valve size	
19 mm	3.6% (24/675)
21 mm	18.4% (124/675)
23 mm	31.3% (211/675)
25 mm	28.0% (189/675)
27 mm	7.3% (49/675)
29 mm	0.4% (3/675)
Other‡	11.1% (75/675)
Total aortic cross clamp time (min)	68.6 ± 28.9
Total time in catheterization laboratory or operating room (min)	276.6 ± 79.5
SAVR approach	

Procedure Data	Summary Statistics*
	SAVR (N=678)
Full sternotomy	65.9% (446/677)
Mini sternotomy	14.5% (98/677)
Right anterior thoracotomy	19.4% (131/677)
Other	0.3% (2/677)
Concomitant procedures§	
Aortic root enlargement	1.6% (11/678)
Coronary artery bypass grafting (CABG)	13.6% (92/678)
Permanent pacemaker implantation	0.0% (0/678)
Surgical treatment of atrial fibrillation	3.5% (24/678)
Automatic implantable cardioverter-defibrillator (AICD) implantation	0.0% (0/678)
Left atrial appendage (LAA) closure	6.2% (42/678)
Patent foramen ovale (PFO) closure	0.7% (5/678)
Mitral valve repair	0.6% (4/678)
Mitral valve replacement	0.0% (0/678)
Other	5.0% (34/678)
Length of index hospitalization (days)	6.2 ± 3.3

*Continuous measures - mean ± SD (n); categorical measures - % (no./Total no.).
†Adjudicated by CEC: Aborted procedure or SAVR conversion to alternate procedure.
‡Others included sutureless valves categorized as "S," "M," or "L" for valve size.
§Subjects might have more than one concomitant procedure.

CT Substudy

There were 197 TAVR and 177 SAVR patients at 30 days and 112 and 94 patients at 12 months, respectively, who had an adequate CT for leaflet assessments at both time points. The HALT and leaflet mobility imaging findings are summarized in Table 11, along with the associated mean aortic pressure gradients. The mean aortic pressure gradients at 12 months stratified by HALT and leaflet mobility at 30 days are summarized in Table 12 and Table 13, respectively. The rate of death, stroke or TIA at 1 year stratified by HALT and leaflet mobility at 30 days are summarized in Table 14 and Table 15, 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 11: HALT and Leaflet Mobility Findings and Associated Mean Gradients

Findings	Summary Statistics*			
	At 30 Days		At 12 Months	
	TAVR (N=197)	SAVR (N=177)	TAVR (N=112)	SAVR (N=94)
Proportion of patients on oral anticoagulants at time of scan†	9.1% (18/197)	22.0% (39/177)	12.5% (14/112)	10.6% (10/94)
HALT‡				
No HALT (no thickening)	82.2% (162/197)	87.6% (155/177)	70.5% (79/112)	75.5% (71/94)
Mean gradient (mmHg)	8.6 ± 3.6 (160)	10.5 ± 3.6 (153)	8.2 ± 3.2 (77)	11.4 ± 4.6 (69)
Presence of HALT	17.8% (35/197)	12.4% (22/177)	29.5% (33/112)	24.5% (23/94)
<25% leaflet length thickened	10.7% (21/197)	2.3% (4/177)	17.0% (19/112)	6.4% (6/94)
Mean gradient (mmHg)	7.2 ± 3.0 (21)	9.2 ± 4.6 (4)	8.4 ± 2.5 (19)	8.6 ± 2.5 (6)
25%-50% leaflet length thickened	3.0% (6/197)	4.5% (8/177)	7.1% (8/112)	8.5% (8/94)
Mean gradient (mmHg)	8.1 ± 1.6 (6)	11.1 ± 3.8 (8)	7.2 ± 2.4 (7)	10.4 ± 4.1 (8)
50%-75% leaflet length thickened	2.0% (4/197)	3.4% (6/177)	3.6% (4/112)	6.4% (6/94)
Mean gradient (mmHg)	6.8 ± 3.0 (2)	12.2 ± 5.6 (6)	7.9 ± 4.9 (4)	11.9 ± 3.9 (6)
>75% leaflet length thickened	2.0% (4/197)	1.7% (3/177)	1.8% (2/112)	3.2% (3/94)
Mean gradient (mmHg)	5.9 ± 1.4 (4)	6.9 ± 3.5 (3)	11.6 ± NA (1)	10.0 ± 2.3 (3)
Number of leaflets with HALT				
0 leaflet	82.2% (162/197)	87.6% (155/177)	70.5% (79/112)	75.5% (71/94)
1 leaflet thickening	11.7% (23/197)	5.1% (9/177)	13.4% (15/112)	13.8% (13/94)
2 leaflets thickening	5.1% (10/197)	5.1% (9/177)	12.5% (14/112)	8.5% (8/94)

Findings	Summary Statistics*			
	At 30 Days		At 12 Months	
	TAVR (N=197)	SAVR (N=177)	TAVR (N=112)	SAVR (N=94)
3 leaflets thickening	1.0% (2/197)	2.3% (4/177)	3.6% (4/112)	2.1% (2/94)
Leaflet mobility§				
Unrestricted	84.6% (148/175)	89.0% (153/172)	70.6% (77/109)	77.5% (69/89)
Mean gradient (mmHg)	8.6 ± 3.7 (146)	10.5 ± 3.6 (151)	8.2 ± 3.2 (76)	11.3 ± 4.6 (67)
Partially restricted (<25%)	9.7% (17/175)	5.2% (9/172)	20.2% (22/109)	7.9% (7/89)
Mean gradient (mmHg)	7.6 ± 3.2 (17)	9.6 ± 3.4 (9)	8.3 ± 2.6 (22)	7.7 ± 2.7 (7)
Partially restricted (25%-50%)	3.4% (6/175)	4.1% (7/172)	6.4% (7/109)	10.1% (9/89)
Mean gradient (mmHg)	7.0 ± 2.1 (5)	12.8 ± 5.5 (7)	8.0 ± 2.0 (6)	11.8 ± 3.7 (9)
Partially restricted (50%-75%)	1.7% (3/175)	1.2% (2/172)	1.8% (2/109)	3.4% (3/89)
Mean gradient (mmHg)	7.8 ± 1.6 (2)	10.6 ± 6.3 (2)	9.8 ± 6.8 (2)	12.4 ± 3.4 (3)
Largely immobile	0.6% (1/175)	0.6% (1/172)	0.9% (1/109)	1.1% (1/89)
Mean gradient (mmHg)	5.9 ± NA (1)	9.7 ± NA (1)	NA (0)	11.0 ± NA (1)
Number of leaflets partially restricted or largely immobile				
0 leaflet	84.6% (148/175)	89.0% (153/172)	70.6% (77/109)	77.5% (69/89)
1 leaflet	10.3% (18/175)	4.1% (7/172)	13.8% (15/109)	12.4% (11/89)
2 leaflets	4.0% (7/175)	4.7% (8/172)	11.9% (13/109)	7.9% (7/89)

Findings	Summary Statistics*			
	At 30 Days		At 12 Months	
	TAVR (N=197)	SAVR (N=177)	TAVR (N=112)	SAVR (N=94)
3 leaflets	1.1% (2/175)	2.3% (4/172)	3.7% (4/109)	2.2% (2/89)

*Continuous measures - mean ± SD (n); categorical measures - % (no./total no.). The analysis population for the 30-day analysis included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days; the analysis population for the 12-month analysis had an adequate CT for leaflet assessments at both time points.
†During the course of the substudy enrollment, a protocol amendment removed the requirement for discontinuation of anticoagulation therapy prior to the CT scan at 30 days.
‡HALT was defined as: the presence of any hypoattenuated 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%, >75%. If more than one leaflet had the appearance of HALT, the thickening measure of the most impacted leaflet was used. One SAVR subject was identified as having one thickened leaflet; however, the extent of thickening was not recorded, and the percentages do not sum to 100%.
§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 immobility any degree of restriction or immobility on any one leaflet rendered a finding.

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

	Summary Statistics*			
	No HALT at 30 Days		HALT at 30 Days	
	TAVR (N=162)	SAVR (N=155)	TAVR (N=35)	SAVR (N=22)
Mean gradient	8.1 ± 2.9 (112)	11.5 ± 4.4 (93)	6.8 ± 3.4 (18)	10.1 ± 3.8 (17)

*Mean ± SD (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: Mean Aortic Gradient at 1 Year Stratified by Leaflet Mobility at 30 Days

	Summary Statistics*			
	Unrestricted at 30 Days		Reduced Leaflet Mobility at 30 Days	
	TAVR (N=148)	SAVR (N=153)	TAVR (N=27)	SAVR (N=19)
Mean gradient	7.9 ± 2.7 (98)	11.5 ± 4.5 (91)	6.5 ± 3.6 (14)	10.5 ± 3.8 (15)

*Mean ± SD (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 14: All-Cause Mortality, All Stroke or TIA at 1 Year Stratified by HALT at 30 Days

1-Year Endpoint	Kaplan-Meier Rate*			
	No HALT at 30 Days		HALT at 30 Days	
	TAVR (N=162)	SAVR (N=155)	TAVR (N=35)	SAVR (N=22)
All-cause mortality	0.0% (0, 0)	0.9% (1, 1)	0.0% (0, 0)	4.5% (1, 1)
All stroke	2.5% (4, 4)	1.9% (3, 3)	2.9% (1, 2)	0.0% (0, 0)
TIA	1.9% (3, 3)	0.0% (0, 0)	5.7% (2, 2)	0.0% (0, 0)
All-cause mortality or all stroke or TIA	4.3% (7, 7)	2.8% (4, 4)	8.6% (3, 4)	4.5% (1, 1)

*Kaplan-Meier rate (# patients, # events). 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 procedure 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 15: All-Cause Mortality, All Stroke or TIA at 1 Year Stratified by Leaflet Mobility at 30 Days

1-Year Endpoint	Kaplan-Meier Rate*			
	Unrestricted at 30 Days		Reduced Leaflet Mobility at 30 Days	
	TAVR (N=148)	SAVR (N=153)	TAVR (N=27)	SAVR (N=19)
All-cause mortality	0.0% (0, 0)	0.9% (1, 1)	0.0% (0, 0)	5.3% (1, 1)
All stroke	2.7% (4, 4)	2.0% (3, 3)	3.7% (1, 2)	0.0% (0, 0)
TIA	1.4% (2, 2)	0.0% (0, 0)	7.4% (2, 2)	0.0% (0, 0)
All-cause mortality or all stroke or TIA	4.1% (6, 6)	2.8% (4, 4)	11.1% (3, 4)	5.3% (1, 1)

*Kaplan-Meier rate (# patients, # events). 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 procedure date as the start date in determining time to event. The 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 conducting clinical studies covered by the regulation. The pivotal clinical study included 1032 investigators, of which none were full-time or part-time employees of the sponsor and 46 had disclosable financial interests/arrangements related to the Low Risk study as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 12
- Significant payment of other sorts: 34
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 2

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 12 months. On average, the EOA increased from 0.8 cm^2 at baseline to 2.2 cm^2 at 12 months, and the mean pressure gradient decreased from 44.8 mmHg at baseline to 8.7 mmHg at 12 months 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 4.6% at 12 months, while in the SAVR cohort, the proportion was 1.4% at 12 months. The proportion of patients with paravalvular AR ≥ moderate was 4.0% at 12 months, as compared to 0.8% at 12 months in the SAVR cohort.

The improvement in valve hemodynamics in the TAVR patients was further demonstrated through improvements in NYHA classification and QoL. In the TAVR cohort, about 1.7% of the patients were in NYHA Class III or IV at 12 months as compared to 25.1% at baseline; similar results were seen in the SAVR cohort. In addition, clinically significant improvement in the KCCQ overall summary score was observed in the TAVR patients, which increased from 68.7 at baseline to 88.7 and 90.5 at 30 days and 12 months, respectively. Furthermore, the mean total time in the catheterization laboratory or operating room and index procedure hospital stay were 148.2 minutes and 2.6 days, respectively, for TAVR, which were significantly longer for SAVR (276.6 minutes and 6.2 days, respectively).

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in the 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 the device is suitable for long-term implant.

The posterior median estimate of all-cause mortality or disabling stroke at 24 months (i.e., the primary endpoint) was 5.3% for TAVR and 6.7% for SAVR. TAVR with the

Evolut R or Evolut PRO TAV was found to be non-inferior to SAVR in the primary endpoint within a non-inferiority margin of 6% with a posterior probability of >0.999. The K-M rate of all stroke at 30 days was 3.5% for TAVR and 3.3% for SAVR, while the rates of disabling stroke were 0.4% and 1.6%, respectively. The K-M rate of all-cause mortality for TAVR was 0.4% at 30 days, 2.2% at 12 months, and 4.0% at 24 months, as compared to 1.2%, 2.8%, and 3.6%, respectively, for SAVR.

The CT substudy revealed that 17.8% and 29.5% of TAVR patients had various degree of leaflet thickening at 30 days and 12 months, respectively, as compared to 12.4% and 24.5% of SAVR patients. In addition, various degrees of restricted leaflet mobility were observed in 15.4% of patients at 30 days and 29.4% of patients at 12 months in the TAVR cohort, which was 11.0% and 22.5%, 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 Evolut R or Evolut PRO TAV include improved valve hemodynamic performance, improved functional status as measured by the NYHA classification, and improved QoL at 1 year post-procedure.

The probable risks of TAVR with the Evolut R or Evolut PRO TAV include procedure-related complications such as death, stroke, myocardial infarction, major vascular complications, bleeding, conduction disturbance, and acute kidney injury.

1. Patient Perspectives

   This application did not include specific information on patient perspectives for TAVR with the Evolut R or Evolut PRO TAV. However, since TAVR provides a less invasive alternative to SAVR, FDA believes that many patients would prefer the TAVR therapy. However, the long-term durability of the Evolut R or Evolut PRO TAV compared to surgically implanted valves have 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 Evolut R or Evolut PRO TAV outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Evolut R System and Evolut PRO System for the replacement of native aortic valves in symptomatic severe aortic stenosis patients who are deemed to be at low surgical risk.

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 Medtronic CoreValve Evolut R System and CoreValve Evolut PRO System "Low Risk" Indication Premarket Pivotal Cohort**: The study will consist of all living patients who were enrolled in the pivotal cohort 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, acute kidney injury at stage 2 or 3, 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, KCCQ score, and hemodynamic performance metrics by Doppler echocardiography.

2. **Medtronic CoreValve Evolut R System and CoreValve Evolut PRO 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 Medtronic CoreValve Evolut R System and CoreValve Evolut PRO 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 Medtronic CoreValve Evolut R System and CoreValve Evolut PRO 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.