

## SUMMARY OF SAFETY AND EFFECTIVENESS DATA

### I. GENERAL INFORMATION

Device Generic Name: Aortic valve, prosthesis, percutaneously delivered

Device Trade Name: Medtronic CoreValve™ System: Transcatheter Aortic Valve (23, 26, 29, and 31 mm); Delivery Catheter System; and Compression Loading System

Medtronic CoreValve™ Evolut™ R System: CoreValve Evolut R Transcatheter Aortic Valve (23, 26, 29, and 34 mm); EnVeo R Delivery Catheter System; and EnVeo R Compression Loading

Medtronic CoreValve™ Evolut™ PRO System: CoreValve Evolut PRO Transcatheter Aortic Valve (23, 26, and 29 mm); EnVeo R Delivery Catheter System; and EnVeo R Compression Loading System

Device Prococode: 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/S033

Date of FDA Notice of Approval: July 10, 2017

The original PMA of the Medtronic CoreValve System, P130021, was approved on January 17, 2014, and the indication was later expanded in Panel Track PMA Supplements P130021/S002 and P130021/S010 on June 12, 2014, and March 30, 2015, respectively, with a combined indication for use in patients with symptomatic heart disease due to either severe native calcific aortic stenosis or 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., Society of Thoracic Surgeons operative risk score  $\geq 8\%$  or at a  $\geq 15\%$  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](http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021b.pdf)

- P130021/S002:  
[http://www.accessdata.fda.gov/cdrh\\_docs/pdf13/P130021S002b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021S002b.pdf)
- P130021/S010:  
[http://www.accessdata.fda.gov/cdrh\\_docs/pdf13/P130021S010B.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021S010B.pdf)

The CoreValve Evolut R System and the CoreValve Evolut PRO System are design iterations of the CoreValve System. The former 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; the latter was approved under P130021/S029 on March 20, 2017.

The current supplement was submitted to expand the indication of the CoreValve System, CoreValve Evolut R System, and CoreValve Evolut PRO System to include patients with severe native calcific aortic stenosis who are deemed to be at intermediate risk for surgical aortic valve replacement (SAVR).

## **II. INDICATIONS FOR USE**

The Medtronic CoreValve, CoreValve Evolut R, CoreValve Evolut PRO systems are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality  $\geq 3\%$  at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical comorbidities unmeasured by the STS risk calculator).

## **III. CONTRAINDICATIONS**

The Medtronic CoreValve, CoreValve Evolut R, CoreValve Evolut PRO systems are contraindicated for patients presenting with any of the following conditions:

- Known hypersensitivity or contraindication to aspirin, heparin (HIT/HITTS) and bivalirudin, ticlopidine, clopidogrel, Nitinol (Titanium or Nickel), or sensitivity to contrast media, which cannot be adequately premedicated
- Ongoing sepsis, including active endocarditis
- Pre-existing mechanical heart valve in aortic position

## **IV. WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the Medtronic CoreValve, CoreValve Evolut R, and CoreValve Evolut PRO systems labeling.

## **V. DEVICE DESCRIPTION**

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

- **Medtronic CoreValve System**

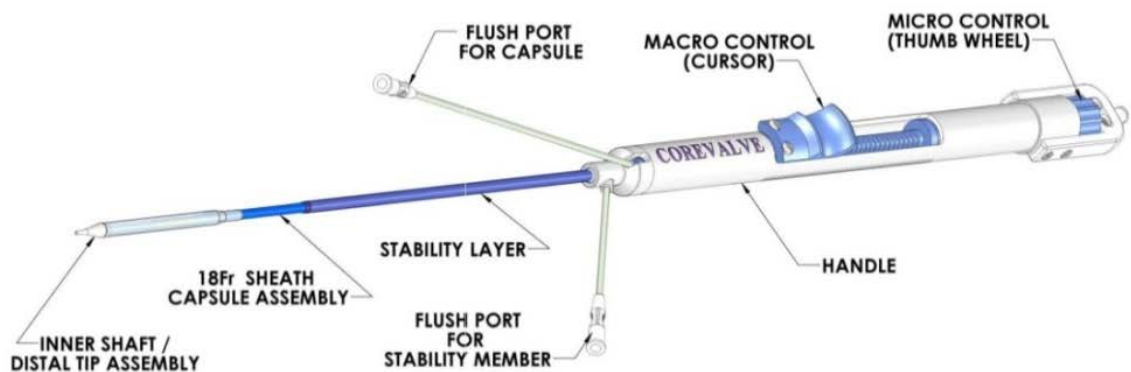
The CoreValve TAV, as shown in Figure 1, is comprised of a self-expanding, multi-level, radiopaque Nitinol frame, a trileaflet porcine pericardial tissue valve, and a porcine pericardial skirt. The porcine pericardial tissue is processed with alpha-amino oleic acid (AOA<sup>®</sup>), which is an antimineralization treatment derived from oleic acid, a naturally occurring long-chain fatty acid.

**Figure 1: CoreValve Transcatheter Aortic Valve**



The DCS with AccuTrak stability layer (AccuTrak DCS), as shown in Figure 2, is used to deploy the TAV. The TAV is loaded within the capsule featuring an atraumatic, radiopaque tip and protective sheath. The AccuTrak stability layer is fixed at the handle and extends down the outside of the catheter shaft to provide a barrier between the catheter and vessel walls. The handle features macro and micro adjustment control of the retractable capsule sheath.

**Figure 2: CoreValve Delivery Catheter System**



The CLS, as shown in Figure 3, is a system of reduction cones and tubing designed to compress the TAV to an optimal diameter for manual loading into the DCS. It comprises the following elements:

1. Inflow tube (straight tube)
2. Outflow cone

3. Outflow cap
4. Outflow tube (tube with flared ends)
5. Inflow cone

**Figure 3: CoreValve Compression Loading System**



- **Medtronic CoreValve Evolut R System**

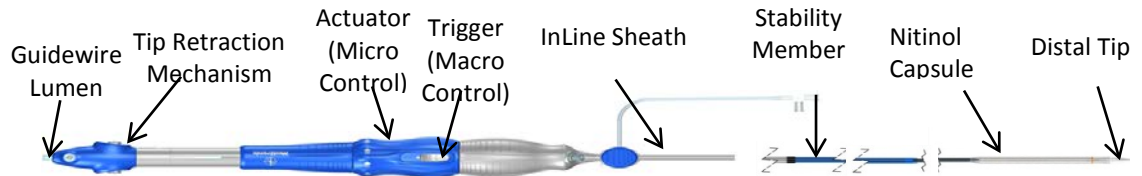
The CoreValve Evolut R TAV, as shown in Figure 4, is a design iteration of the CoreValve TAV. It provides the optional capability of allowing for resheathing and/or complete recapture and redeployment during valve deployment. The Evolut R TAV is fully functional at approximately 2/3 partial deployment from the DCS. Once the TAV is fully deployed, it is not retrievable from the site of implantation.

**Figure 4: Evolut R Transcatheter Aortic Valves**



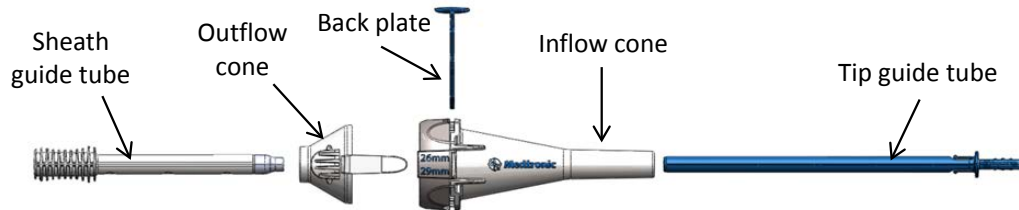
The EnVeo R DCS used with the Evolut R TAV is a single use, intravascular, over-the-wire delivery catheter, as shown in Figure 5. It is designed to be compatible with commercially available 0.035" intravascular wires. The DCS incorporates a protective deployment sheath that houses and deploys the prosthesis.

**Figure 5: EnVeo R Delivery Catheter System**



The EnVeo R Loading System (LS) used with the Evolut R TAV is shown in Figure 6.

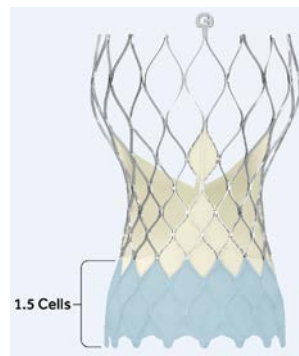
**Figure 6: EnVeo R Loading System)**



- **Medtronic CoreValve Evolut PRO System**

The CoreValve Evolut PRO TAV, as shown in Figure 7, is a design iteration of the CoreValve 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 leak (PVL).

**Figure 7: Evolut PRO Transcatheter Aortic Valve**



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

## **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

There are several other alternatives for the correction of symptomatic severe native calcific aortic stenosis in patients deemed to be at intermediate risk for open surgical therapy, including SAVR, treatment with other approved TAVR therapy, 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 is currently commercially available for the “intermediate risk” transcatheter aortic valve replacement (TAVR) indication in the following 44 countries and has not been withdrawn from marketing for any reason related to its safety or effectiveness:

- Austria
- Belgium
- Belarus
- Croatia
- Cyprus
- Czech Republic
- Denmark
- Egypt\*
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Iceland
- Indonesia\*
- Ireland
- Israel\*
- Italy
- Kazakhstan\*
- Latvia
- Lithuania
- Luxembourg
- Macedonia
- Malaysia
- Malta
- Mexico
- Netherlands
- Norway
- Poland
- Portugal
- Romania
- Saudi Arabia
- Serbia
- Slovakia (Slovak Republic)
- Slovenia
- Spain
- Sweden
- Switzerland
- Taiwan\*
- Thailand\*
- Turkey
- United Kingdom
- Vietnam\*

The Medtronic CoreValve System and CoreValve Evolut PRO System have not been marketed in the United States or any foreign country for the “intermediate risk” 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 System, CoreValve Evolut R System, and CoreValve Evolut PRO System:

- Death
- Cardiac arrest
- Coronary occlusion, obstruction, or vessel spasm (including acute coronary closure)
- Emergent surgery (e.g., coronary artery bypass, heart valve replacement, valve explant)

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\*23, 26, and 29 mm valve sizes only.

- Multi-organ failure
- Heart failure
- Myocardial infarction (MI)
- Cardiogenic shock
- Respiratory insufficiency or respiratory failure
- Cardiovascular injury (including rupture, perforation, or dissection of vessels, ventricle, myocardium, or valvular structures that may require intervention)
- Ascending aorta trauma
- Cardiac tamponade
- Cardiac failure or low cardiac output
- Prosthetic valve dysfunction including, but not limited to, fracture; bending (out-of-round configuration) of the valve frame; under-expansion 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; regurgitation; stenosis
- Thrombosis/embolus (including valve thrombosis)
- Valve migration/valve embolization
- Ancillary device embolization
- Emergent percutaneous coronary intervention (PCI)
- Emergent balloon valvuloplasty
- Major or minor bleeding that may or may not require transfusion or intervention (including life-threatening or disabling bleeding)
- Allergic reaction to antiplatelet agents, contrast medium, or anesthesia
- Infection (including septicemia and endocarditis)
- Stroke, transient ischemic attack (TIA), or other neurological deficits
- Permanent disability
- Renal insufficiency or renal failure (including acute kidney injury)
- Mitral valve regurgitation or injury
- Tissue erosion
- Vascular access related complications (e.g., dissection, perforation, pain, bleeding, hematoma, pseudoaneurysm, irreversible nerve injury, compartment syndrome, arteriovenous fistula, stenosis)
- Conduction system disturbances (e.g., atrioventricular node block, left-bundle branch block, asystole), which may require a permanent pacemaker
- Cardiac arrhythmias
- Encephalopathy
- Pulmonary edema
- Pericardial effusion
- Pleural effusion
- Myocardial ischemia
- Peripheral ischemia
- Bowel ischemia
- Heart murmur

- Hemolysis
- Cerebral infarction-asymptomatic
- Non-emergent reoperation
- Inflammation
- Fever
- Hypotension or hypertension
- Syncope
- Dyspnea
- Anemia
- Angina
- Abnormal lab values (including electrolyte imbalance)

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 Medtronic CoreValve System and CoreValve Evolut R System for patients with symptomatic severe native calcific aortic stenosis deemed to be at intermediate risk for open surgical therapy in the US, Canada, and Europe (Spain, Denmark, the Netherlands, Switzerland, the United Kingdom, Sweden and Germany) under IDE #G120169 (entitled the “SURTAVI” trial). Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

The Medtronic CoreValve Evolut PRO System was not used in the trial. However, the results obtained on the CoreValve System and CoreValve Evolut R System are considered applicable to the CoreValve Evolut PRO System based on prior demonstration of device comparability in application P130021/S029.

### **A. Study Design**

Patients were enrolled between June 19, 2012, and June 30, 2016. The database for this Panel Track Supplement reflected data collected through October 20, 2016, and included 1746 randomized patients. There were 87 investigational sites.

The SURTAVI trial was a prospective, randomized (1:1), unblinded, multi-center investigational study intended to determine whether TAVR is non-inferior to SAVR (within an absolute margin,  $\delta$ , of 0.07) 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 2000, including the roll-in subjects. The trial employed



Bayesian adaptive methods to allow for “early win” look when 1400 subjects reached 12 months of follow-up. At the “early win” analysis, if the posterior probability,  $P(H_{A,\delta=0.07}|\text{data})$ , is greater than 0.971, non-inferiority would be declared at this time; otherwise, all 1600 subjects would be followed to 24 months when a “final win” look would occur. At the “final win” analysis, the standard for trial success would again be  $P(H_{A,\delta=0.07}|\text{data}) > 0.971$ .

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, which participated in source data verification.

## 1. Clinical Inclusion and Exclusion Criteria

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

- Subject must have co-morbidities such that Heart Team agrees predicted risk of operative mortality is  $\geq 3\%$  and  $< 15\%$  at 30 days (Intermediate Clinical Risk classification). Heart Team evaluation of clinical surgical mortality risk for each patient includes the calculated STS score for predicted risk of surgical mortality augmented by consideration of the overall clinical status and co-morbidities unmeasured by the STS risk calculation.
- Heart Team unanimously agrees on treatment proposal and eligibility for randomization based on their clinical judgment (including anatomy assessment, risk factors, etc.).
- Subject has severe aortic stenosis presenting with:
  - Critical aortic valve area defined as an initial aortic valve area of  $\leq 1.0 \text{ cm}^2$  or aortic valve area index  $< 0.6 \text{ cm}^2/\text{m}^2$ , AND
  - Mean gradient  $> 40 \text{ mmHg}$  or  $V_{\text{max}} > 4 \text{ m/sec}$  by resting echocardiogram or simultaneous pressure recordings at cardiac catheterization [or with dobutamine stress, if subject has a left ventricular ejection fraction (LVEF)  $< 55\%$ ] or velocity ratio  $< 0.25$ .
- Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater.
- Subject and the treating physician agree that the subject will return for all required post procedure follow-up visits.
- Subject meets the legal minimum age to provide informed consent based on local regulatory requirements.

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

- Subject has refused SAVR as a treatment option.

- Any condition considered a contraindication for placement of a bioprosthetic valve (i.e., subject requires a mechanical valve).
- A known hypersensitivity or contraindication to all anticoagulation/antiplatelet regimens (including inability to be anticoagulated for the index procedure), Nitinol, or sensitivity to contrast media which cannot be adequately pre-medicated.
- Blood dyscrasias as defined: leukopenia (WBC <1000 mm<sup>3</sup>), thrombocytopenia (platelet count <50,000 cells/mm<sup>3</sup>), history of bleeding diathesis or coagulopathy.
- Ongoing sepsis, including active endocarditis.
- Any condition considered a contraindication to extracorporeal assistance.
- Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to randomization (Subjects with recent placement of drug eluting stent(s) should be assessed for ability to safely proceed with SAVR within the protocol timeframe).
- Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within six weeks of randomization.
- Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.
- Recent (within 6 months of randomization) cerebrovascular accident (CVA) or TIA.
- Active 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).
- Multivessel coronary artery disease with a Syntax score > 22 and/or unprotected left main coronary artery (Syntax score calculation is not required for patients with history of previous revascularization if repeat revascularization is not planned).
- 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 preclude 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 index procedure.
- Need for emergency surgery for any reason.
- True porcelain aorta (i.e., Heart Team agrees the aorta is not clampable for SAVR).
- Extensive mediastinal radiation.
- Liver failure (Child-C).

- Reduced ventricular function with LVEF < 20% as measured by resting echocardiogram.
- Uncontrolled atrial fibrillation (e.g., resting heart rate > 120 bpm).
- Pregnancy or intent to become pregnant prior to completion of all protocol follow-up requirements.
- End stage renal disease requiring chronic dialysis or creatinine clearance < 20 cc/min.
- Pulmonary Hypertension (systolic pressure > 80 mmHg).
- Severe Chronic Obstructive Pulmonary Disease (COPD) demonstrated by Forced Expiratory Volume (FEV1) < 750 cc.
- Frailty assessments - Subject is < 80 years of age and three or more of the following apply OR subject is ≥ 80 years of age and two or more of the following apply:
  - Wheelchair bound
  - Resides in an institutional care facility (e.g., nursing home, skilled care center)
  - Body Mass Index <20 kg/m<sup>2</sup>
  - Grip strength <16 kg
  - Katz Index score ≤ 4
  - Albumin < 3.5 g/dL
- Marfan syndrome or other known connective tissue disease that would necessitate aortic root replacement/intervention.
- Native aortic annulus size < 18 mm or > 29 mm per the baseline diagnostic imaging.
- Pre-existing prosthetic heart valve in any position.
- Mixed aortic valve disease [aortic stenosis and aortic regurgitation with predominant aortic regurgitation (3-4+)].
- Severe mitral or severe tricuspid regurgitation.
- Severe mitral stenosis.
- Hypertrophic obstructive cardiomyopathy;
- Echocardiographic or Multislice Computed Tomography (MSCT) evidence of new or untreated intracardiac mass, thrombus or vegetation;
- Ascending aorta diameter greater than maximum diameter relative to the native aortic annulus size:

Aortic Annulus Diameter	Ascending Aorta Diameter
18 mm – 20 mm	>34 mm
20 mm – 23 mm	>40 mm
23 mm – 29 mm	>43 mm

- Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae):
  - Femoral and left subclavian/axillary access > 70° OR
  - Right subclavian/axillary access: Aortic root angulation > 30°.

- Congenital bicuspid or unicuspid valve verified by echocardiography.
- Sinus of Valsalva anatomy that would prevent adequate coronary perfusion.
- Transarterial access not able to accommodate an 18Fr sheath.

## 2. Follow-Up Schedule

All patients were scheduled for follow-up examinations at discharge or 7 days (whichever came first), 30 days, 6 months, 12 months, 18 months, 24 months and annually thereafter to a minimum of 10 years post procedure. Preoperative and post-operative assessments included physical assessment and patient interview, laboratory measurements, imaging tests, and 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:

$$H_A: \pi_{TAVR} < \pi_{SAVR} + 7\%$$

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

### Secondary Endpoints:

The following ordered list of secondary endpoints, as shown in Table 1, was included 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 NYHA classification from baseline to 12 months (non-inferiority)	$H_A: \mu_{TAVR} > \mu_{SAVR} - 0.375$
#4	Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline to 30 days (non-inferiority)	$H_A: \mu_{TAVR} > \mu_{SAVR} - 5$
#5	Length of index procedure hospital stay (superiority)	$H_A: \mu_{TAVR} < \mu_{SAVR}$
#6	Transvalvular mean gradient at 12 months (superiority)	$H_A: \mu_{TAVR} < \mu_{SAVR}$

<b>Order</b>	<b>Secondary Endpoint</b>	<b>Alternative Hypothesis</b>
#7	EOA at 12 months (superiority)	$H_A: \mu_{TAVR} > \mu_{SAVR}$
#8	Change in KCCQ score from baseline to 30 days (superiority)	$H_A: \mu_{TAVR} > \mu_{SAVR}$
#9	Days alive out of the hospital at 12 months (superiority)	$H_A: \mu_{TAVR} > \mu_{SAVR}$
#10	Days alive out of the hospital at 24 months (superiority)	$H_A: \mu_{TAVR} > \mu_{SAVR}$
#11	Change in SF-36 Physical Summary Scale from baseline to 3 months (superiority)	$H_A: \mu_{TAVR} > \mu_{SAVR}$
#12	Change in EQ-5D from baseline to 3 months (superiority)	$H_A: \mu_{TAVR} > \mu_{SAVR}$
#13	Incidence of major adverse cardiovascular and cerebrovascular events (MACCE) at 30 days or hospital discharge, whichever is longer (superiority)*	$H_A: \pi_{TAVR} < \pi_{SAVR}$
#14	Incidence of major vascular complication at 30 days or hospital discharge, whichever is longer (superiority)	$H_A: \pi_{TAVR} < \pi_{SAVR}$
#15	Incidence of major or life-threatening bleeding events at 30 days or hospital discharge, whichever is longer (superiority)	$H_A: \pi_{TAVR} < \pi_{SAVR}$
#16	Incidence of all strokes at 30 days or hospital discharge, whichever is longer (superiority)	$H_A: \pi_{TAVR} < \pi_{SAVR}$
#17	Incidence of moderate/severe aortic insufficiency at discharge echocardiography (superiority)	$H_A: \pi_{TAVR} < \pi_{SAVR}$
#18	New pacemaker implantation rate for TAVR at 30 days or hospital discharge, whichever is longer	$H_A: \pi_{TAVR} < 30\%$
* MACCE is defined as a composite of all-cause death, myocardial infarction (MI), all stroke, and reintervention (i.e., any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve).		

## **B. Accountability of PMA Cohort**

At the time of database lock, a total of 1746 subjects were randomized in this study, including 879 TAVR subjects and 867 SAVR subjects.

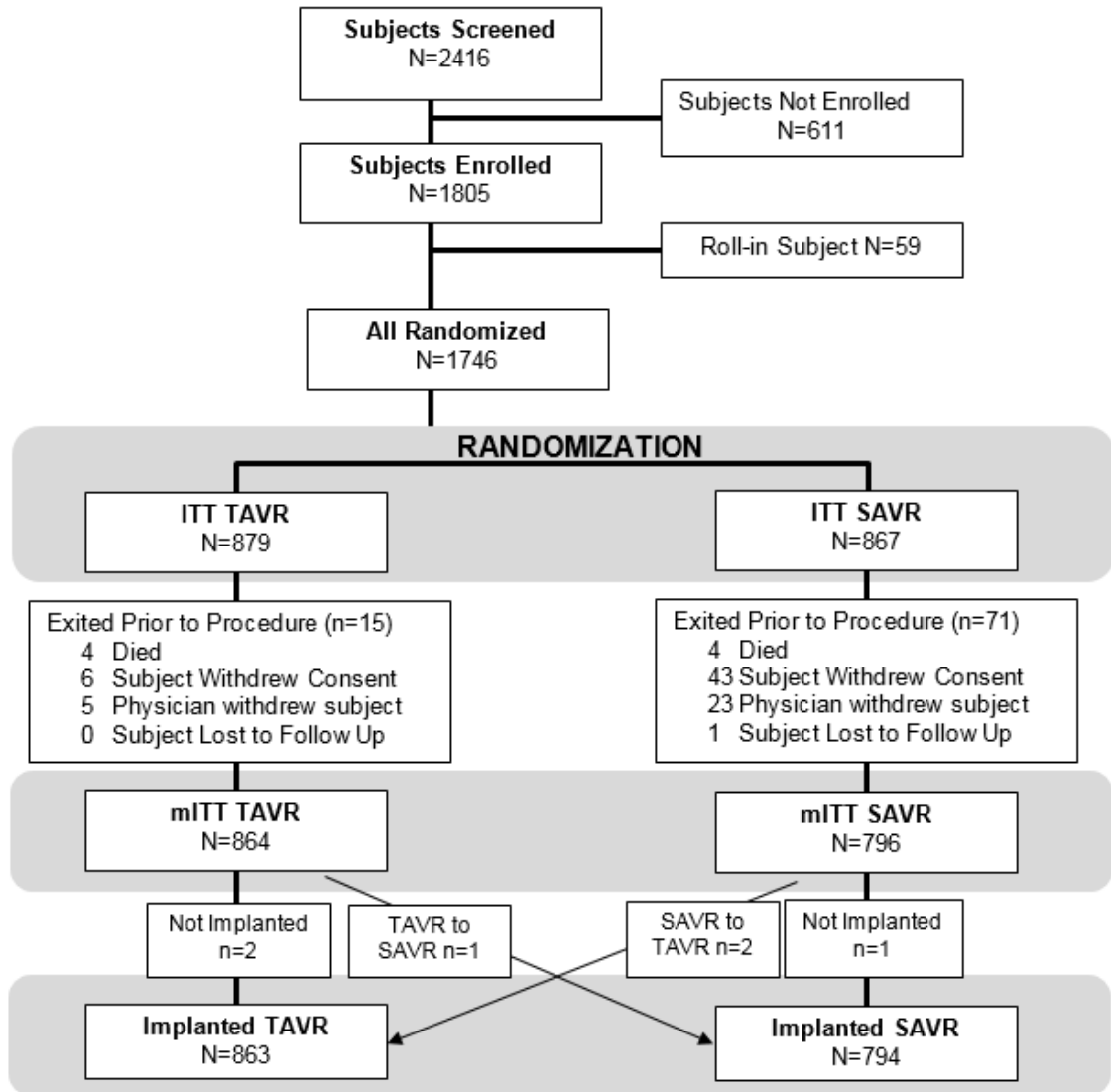
There were three different analysis populations defined in the protocol: intention-to-treat (ITT), modified intention-to-treat (mITT), and implanted (IMP), as summarized in Table 2 and Figure 8. The primary analysis was the mITT analysis.

**Table 2: Analysis Populations**

Analysis Population	Definition	Number of Patients	
		SAVR	TAVR
Intention-to-treat (ITT)	All randomized subjects	867	879
Modified intention-to-treat (mITT)	All ITT subjects with an attempted implant procedure*	796	864
Implanted population	All mITT subjects who were actually implanted with a valve	794	863

\* Attempted implant procedure is defined as when the subject was brought into the procedure room and any of the following had occurred: anesthesia administered, vascular line placed, TEE placed or any monitoring line placed.

**Figure 8: Population Flowchart**



Of the 863 subjects in the Implanted TAVR group, 724 were attempted with the CoreValve System, 139 with the CoreValve Evolut R System.

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

**Table 3: Overall Study Compliance**

Visit Interval	Number Expected*	Visit Completed	Study Exits			
			Died	Withdrew <sup>†</sup>	Lost to Follow-up	Pending Next Visit
<b>SAVR</b>						
Screening	867	100.0%	3	43	1	0
Baseline	820	100.0%	1	23	0	0
Procedure	796	100.0%	3	1	0	0
Discharge	792	99.7%	11	5	0	0
30 days	776	95.7%	24	15	1	22
6 months	714	93.8%	14	10	1	81
12 months	608	90.8%	6	11	1	122
18 months	468	91.0%	15	4	0	142
24 months	307	94.8%	6	6	2	175
<b>TAVR</b>						
Screening	879	100.0%	2	7	0	0
Baseline	870	100.0%	2	4	0	0
Procedure	864	100.0%	6	0	0	0
Discharge	858	99.9%	14	0	0	0
30 days	844	99.4%	16	4	0	25
6 months	799	96.6%	20	10	0	104
12 months	665	93.5%	11	7	0	134
18 months	513	91.8%	12	2	1	151
24 months	347	93.7%	10	7	2	205
*Number expected in an interval = # expected in the previous interval - # died - # withdrew - # lost to follow-up - # pending).						
†Withdrew includes subject withdrew consent and physician withdrew subject from study						

### **C. Study Population Demographics and Baseline Parameters**

The demographics and baseline characteristics of the study population are typical for TAVR study performed in the U.S., as shown in Table 4. The treatment arms were generally well balanced with respect to age, gender, baseline NYHA classification, and the surgical risk scores (STS score and EuroScore).

**Table 4: Patient Demographics and Baseline Characteristics – mITT Population**

Demographics and Baseline Characteristics	Summary Statistics*		
	SAVR	TAVR	Difference (TAVR – SAVR) (95% BCI) <sup>†</sup>
Age (years)	79.7 ± 6.1 (796)	79.9 ± 6.2 (864)	(-0.37, 0.81)
Male	55.0% (438/796)	57.6% (498/864)	(-2.15%, 7.37%)
NYHA Class			
II	41.8% (333/796)	39.8% (344/864)	(-6.71%, 2.72%)
III	51.6% (411/796)	54.6% (472/864)	(-1.80%, 7.78%)
IV	6.5% (52/796)	5.6% (48/864)	(-3.30%, 1.31%)
STS Score (risk of mortality, %)	4.5 ± 1.6 (796)	4.4 ± 1.5 (864)	(-0.28, 0.03)
Logistic EuroScore (%)	11.6 ± 8.0 (795)	11.9 ± 7.6 (864)	(-0.44, 1.06)
Coronary artery disease	64.2% (511/796)	62.6% (541/864)	(-6.20%, 3.05%)
Previous MI	13.9% (111/796)	14.5% (125/864)	(-2.84%, 3.88%)
Previous reintervention			
Coronary artery bypass surgery	17.2% (137/796)	16.0% (138/864)	(-4.83%, 2.34%)
Percutaneous coronary intervention	21.2% (169/796)	21.3% (184/864)	(-3.88%, 3.99%)
Cerebrovascular disease	16.3% (130/796)	17.5% (151/864)	(-2.47%, 4.73%)
Peripheral vascular disease	29.9% (238/796)	30.8% (266/864)	(-3.54%, 5.29%)
Prior stroke	7.2% (57/796)	6.6% (57/864)	(-3.04%, 1.87%)
Chronic lung disease/COPD	33.5% (267/796)	35.4% (305/862)	(-2.74%, 6.39%)
Home oxygen	2.6% (21/795)	2.1% (18/864)	(-2.09%, 0.92%)
Creatinine level > 2 mg/dl	2.1% (17/796)	1.6% (14/864)	(-1.90%, 0.81%)
Atrial fibrillation/atrial flutter	26.5% (211/796)	28.1% (243/864)	(-2.68%, 5.89%)
Permanent pacemaker implantation	9.0% (72/796)	9.7% (84/864)	(-2.14%, 3.47%)
History of hypertension	90.3% (719/796)	92.7% (801/864)	(-0.30%, 5.10%)
Cirrhosis of the liver	0.6% (5/795)	0.5% (4/863)	(-0.99%, 0.60%)
Echocardiographic findings—Implanted Population			
Effective orifice area (cm <sup>2</sup> )	0.8 ± 0.2 (727)	0.8 ± 0.2 (790)	(-0.01, 0.03)
Mean gradient (mmHg)	47.8 ± 13.8 (786)	47.2 ± 14.3 (856)	(-2.03, 0.70)

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

<sup>†</sup>BCI: Bayesian credible interval



## D. Safety and Effectiveness Results

### 1. Primary Endpoint:

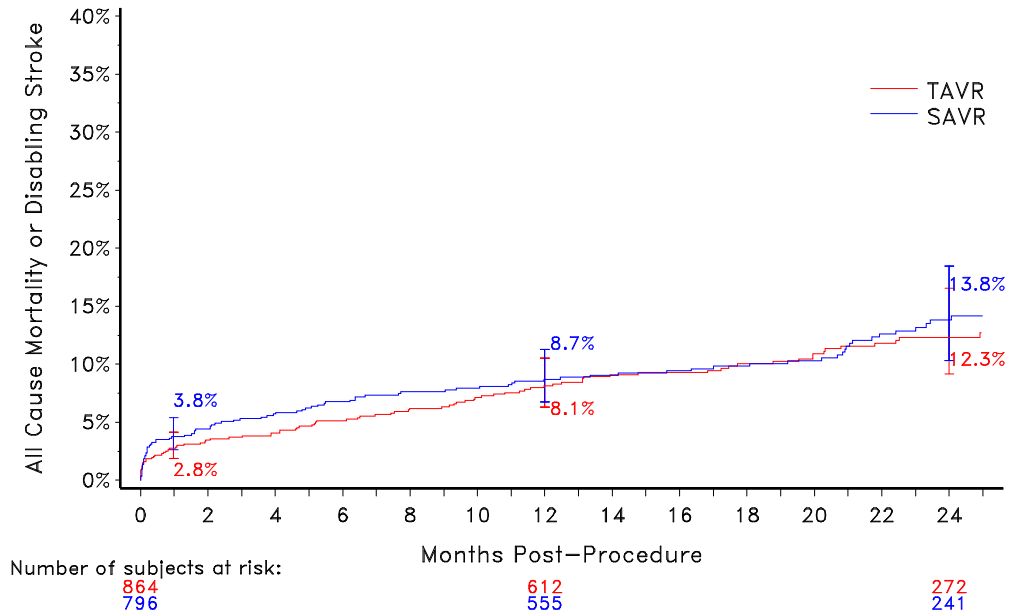
The “early win” assessment of the primary endpoint included all subjects in the mITT population (N = 1660). The median of the posterior distribution for the primary endpoint event rate was 12.6% for the TAVR arm and 14.0% for the SAVR arm, with a median of the posterior distribution of the difference in the primary endpoint event rate (TAVR – SAVR) of -1.4% and a 95% Bayesian credible interval (BCI) of (-5.2%, 2.3%), as summarized in Table 5. The posterior probability of non-inferiority with a margin of 7% was > 0.9999, which is greater than the pre-specified threshold of 0.971, thus the primary endpoint non-inferiority could be concluded.

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

	<b>SAVR (N=796)</b>	<b>TAVR (N=864)</b>
Posterior median (95% BCI)	14.0% (11.4%, 17.0%)	12.6% (10.2%, 15.3%)
Difference (TAVR-SAVR) posterior median (95% BCI)	-1.4% (-5.2%, 2.3%)	
Primary objective – Non-inferiority		
Posterior probability $P(H_{A,\delta=0.07} \text{data})$	> 0.9999	
Posterior threshold for non-inferiority	0.971	
Non-inferiority test	Passed	

The Kaplan-Meier (K-M) curve of all-cause mortality or disabling stroke is shown in Figure 9.

**Figure 9: All-Cause Mortality or Disabling Stroke Rate – mITT 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 primary endpoint hypothesis testing for the ITT and Implanted populations is summarized in Table 6. Non-inferiority was met for both populations.

**Table 6: All-Cause Mortality or Disabling Stroke at 24 Months - ITT and Implanted Populations**

	ITT		Implanted	
	SAVR (N=867)	TAVR (N=879)	SAVR (N=794)	TAVR (N=863)
Posterior median (95% BCI)	14.1% (11.6%, 17.0%)	13.2% (10.8%, 15.8%)	14.2% (11.6%, 17.1%)	12.4% (10.0%, 15.0%)
Difference (TAVR- SAVR) posterior median (95% BCI)	-1.0% (-4.7%, 2.7%)		-1.8% (-5.6%, 1.9%)	
<b>Non-inferiority testing</b>				
Posterior probability $P(H_{A,\delta=0.07}   \text{data})$	>0.9999		>0.9999	
Non-inferiority test	Passed		Passed	

## 2. Secondary Endpoints

### Hypothesis testing:

Hypothesis testing was performed on pre-specified secondary endpoints using a hierarchical test procedure, as shown in Table 7. TAVR was found to be non-inferior to SAVR within the pre-specified non-inferiority margins in terms of the mean gradient and EOA at 12 months, the NYHA functional classification change from baseline to 12 months, and the KCCQ score change from baseline to 30 days. TAVR was determined to be superior to SAVR with respect to the length of index procedure hospital stay, the mean pressure gradient at 12 months, the EOA at 12 months, and the KCCQ score change from baseline to 30-days. However, TAVR was not found to be superior to SAVR with respect to the days alive and out of hospital at 12 months. The remaining secondary endpoints in the hierarchy were not tested.

**Table 7: Secondary Endpoints Hierarchical Testing**

Secondary Endpoint	SAVR Mean $\pm$ SD (N)	TAVR Mean $\pm$ SD (N)	Difference (TAVR-SAVR) (95% BCI)	Posterior Probability Pr( $H_A$   data)	Threshold	Test Result
<b>Non-inferiority testing</b>						
#1 Mean gradient at 12 months	11.7 $\pm$ 5.6 (500)	8.3 $\pm$ 4.0 (590)	(-4.0, -2.8)	1.00	0.95	Passed
#2 EOA at 12 months	1.8 $\pm$ 0.6 (455)	2.2 $\pm$ 0.6 (545)	(0.3, 0.5)	1.00	0.95	Passed
#3 NYHA change (baseline – 12 months)	1.3 $\pm$ 0.8 (508)	1.3 $\pm$ 0.8 (604)	(-0.1, 0.1)	1.00	0.95	Passed
#4 KCCQ summary score change (30 day – baseline)	5.9 $\pm$ 27.0 (700)	18.4 $\pm$ 22.8 (819)	(10.0, 15.1)	1.00	0.95	Passed
<b>Superiority testing</b>						
#5 Length of index procedure hospital stay	9.8 $\pm$ 8.0 (795)	5.8 $\pm$ 4.9 (863)	(-4.7, -3.4)	1.00	0.975	Passed
#6 Mean gradient at 12 months	11.7 $\pm$ 5.6 (500)	8.3 $\pm$ 4.0 (590)	(-4.0, -2.8)	1.00	0.975	Passed
#7 EOA at 12 months	1.8 $\pm$ 0.6 (455)	2.2 $\pm$ 0.6 (545)	(0.3, 0.5)	1.00	0.975	Passed

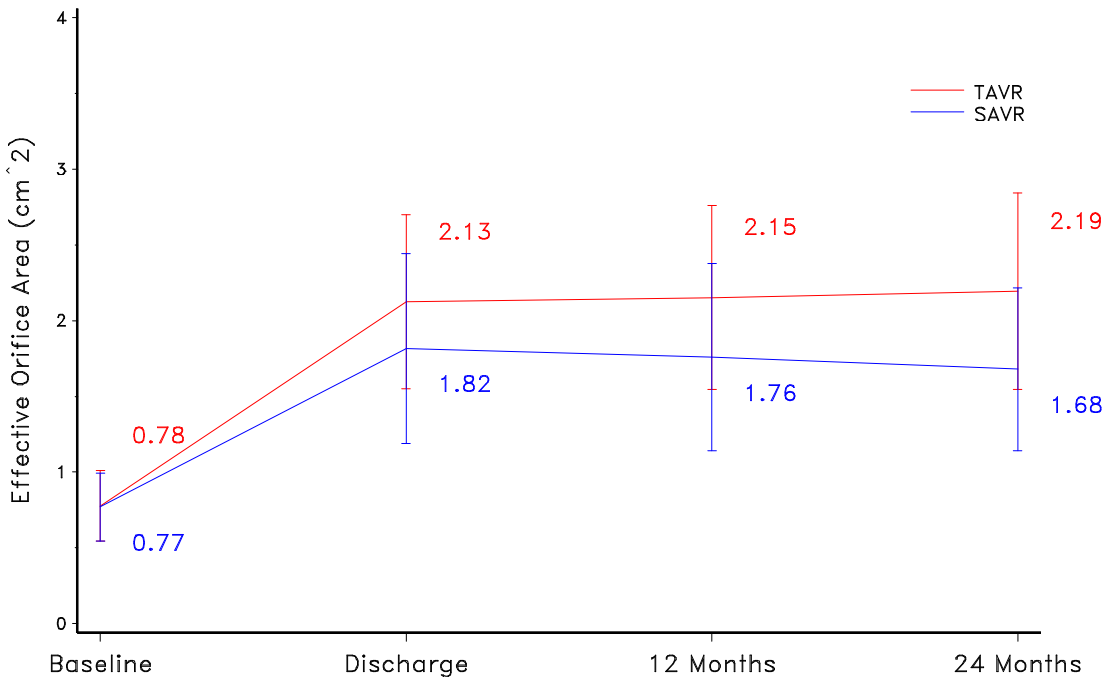
Secondary Endpoint	SAVR Mean $\pm$ SD (N)	TAVR Mean $\pm$ SD (N)	Difference (TAVR-SAVR) (95% BCI)	Posterior Probability Pr( $H_A$   data)	Threshold	Test Result
#8 KCCQ summary score change (30 day – baseline)	5.9 $\pm$ 27.0 (700)	18.4 $\pm$ 22.8 (819)	(10.0, 15.1)	1.00	0.975	Passed

Note: The Implanted population was used for the mean gradient and EOA, and the mITT population for the rest.

Valve Performance:

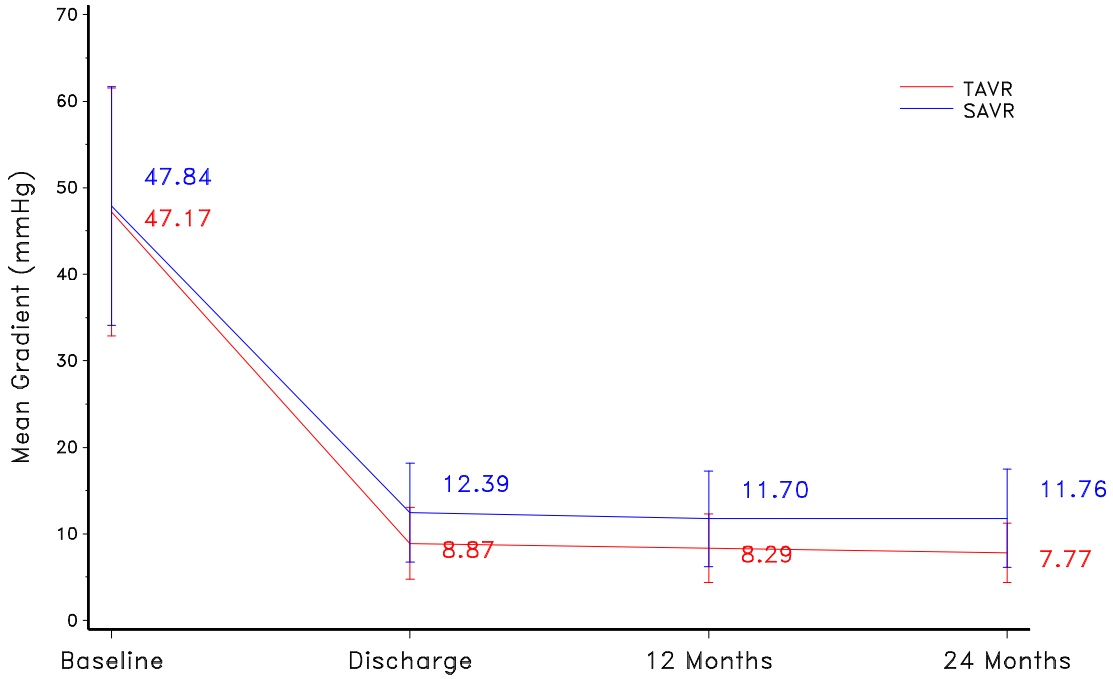
The effective orifice area (EOA), mean aortic gradient, total aortic regurgitation, and paravalvular regurgitation values obtained over time for the TAVR and SAVR subjects in the Implanted population are shown in Figures 10-13. In the TAVR subjects, the mean EOA increased from 0.78 cm<sup>2</sup> at baseline to 2.15 at 12 months, and the mean aortic gradient decreased from 47.17 mmHg to 8.29 mmHg at 12 months. However, at 12 months, 38.9% of the TAVR subjects had greater than trace aortic regurgitation as compared to 10.1% of the SAVR subjects, and 37.2% of the TAVR subjects had greater than trace paravalvular regurgitation as compared to 6.1% of the SAVR subjects.

**Figure 10: Effective Orifice Area (Implanted Population)**



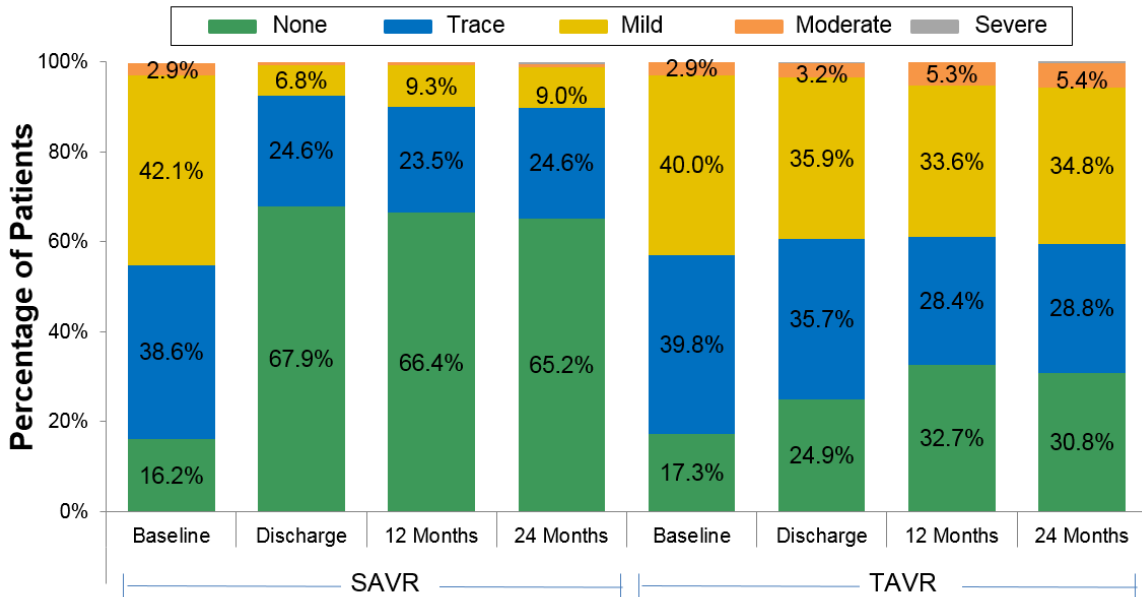
Note: Line plot with mean and standard deviation.

**Figure 11: Mean Aortic Gradient (Implanted Population)**



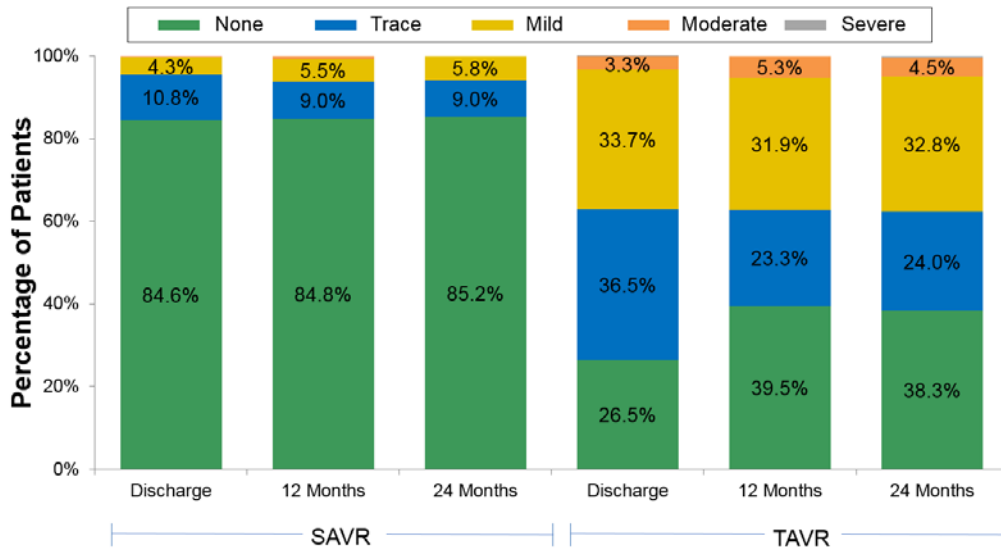
Note: Line plot with mean and standard deviation.

**Figure 12: Total Aortic Regurgitation (Implanted Population)**



Note: Values < 1.0% are not labeled.

**Figure 13: Paravalvular Aortic Regurgitation by Visit (Implanted Population)**

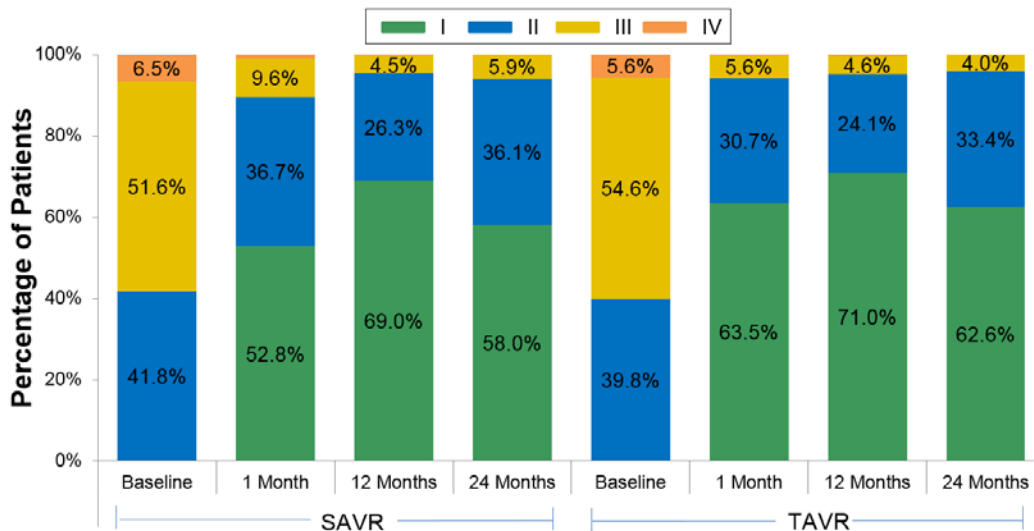


Note: Values < 1.0% are not labeled.

NYHA Functional Class:

The NYHA classifications by visit are presented in Figure 14. In the TAVR mITT population, the percentage of patients in NYHA Class III or IV decreased from 60.2% at baseline to 4.9% at 12 months, while it decreased from 58.2% at baseline to 4.7% at 12 months in the SAVR mITT population.

**Figure 14: NYHA Classification by Visit (mITT Population)**



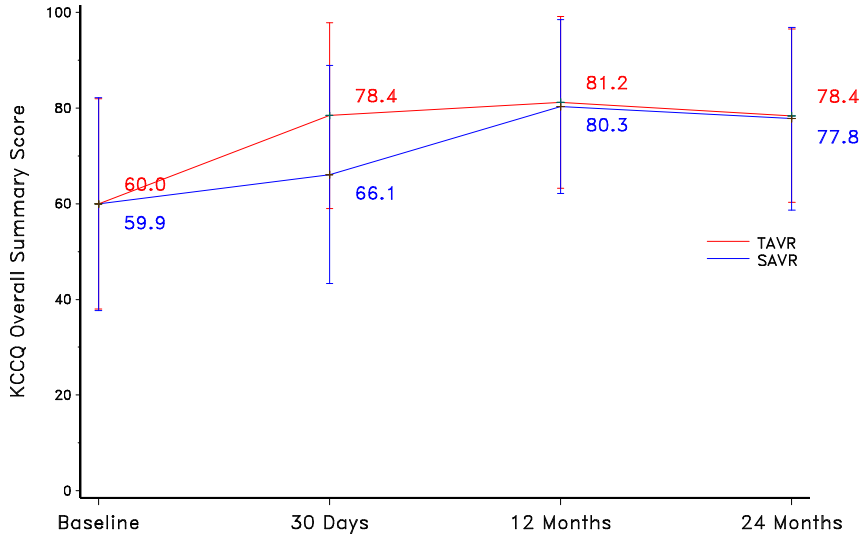
Note: Values < 1.0% are not labeled.

Health Status/QoL Change:

The health status/QoL was measured using the KCCQ, SF-36 Health Status Questionnaire, and EuroQoL (EQ-5D) measure.

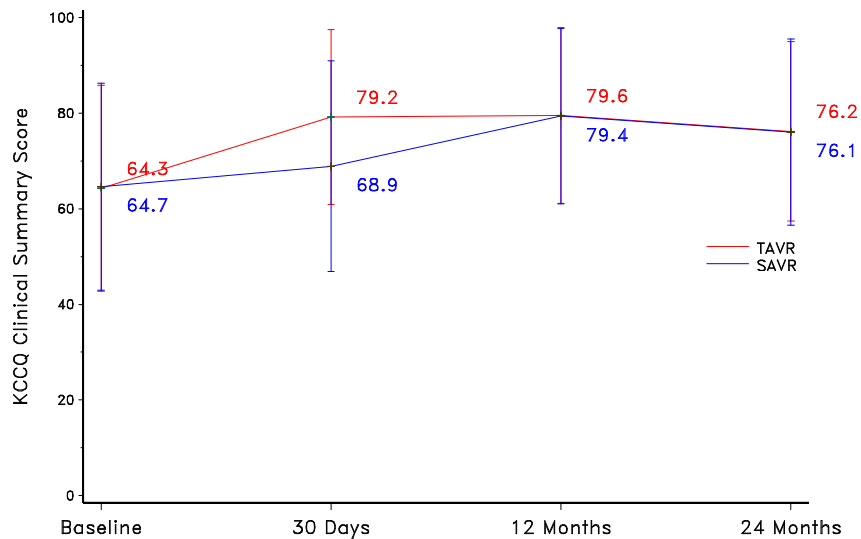
The KCCQ overall and clinical summary scores for the two treatment arms are shown in Figures 15 and 16, respectively.

**Figure 15: KCCQ Overall Summary Score**



Note: Line plot with mean and standard deviation.

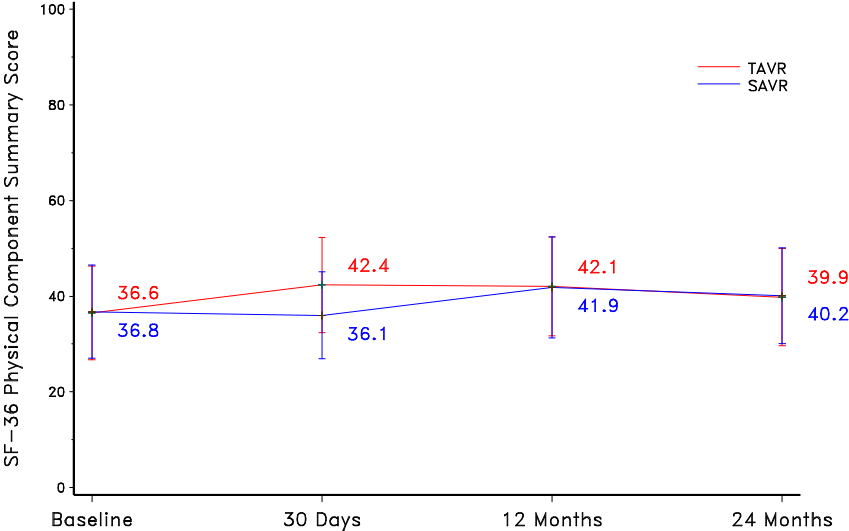
**Figure 16: KCCQ Clinical Summary Score**



Note: Line plot with mean and standard deviation.

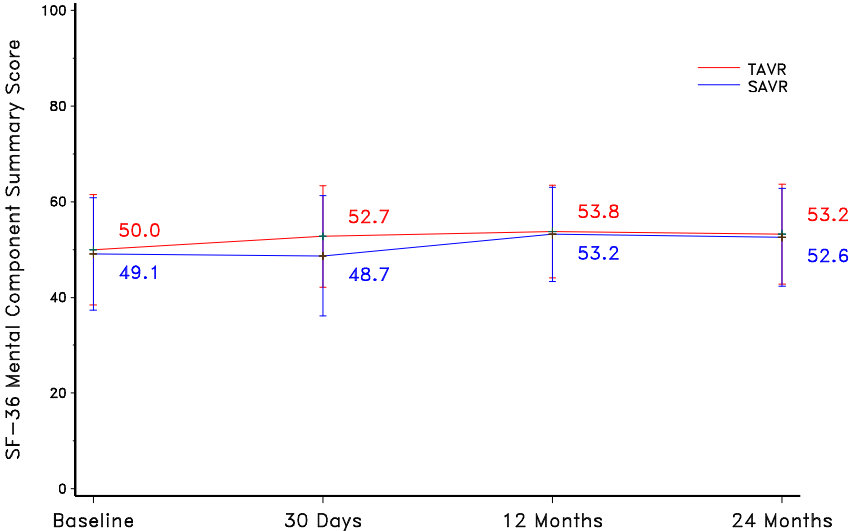
The SF-36 physical and mental component summary scores for the two treatment arms are shown in Figures 17 and 18, respectively.

**Figure 17: SF-36 Physical Component Summary Score**



Note: Line plot with mean and standard deviation.

**Figure 18: SF-36 Mental Component Summary Score**

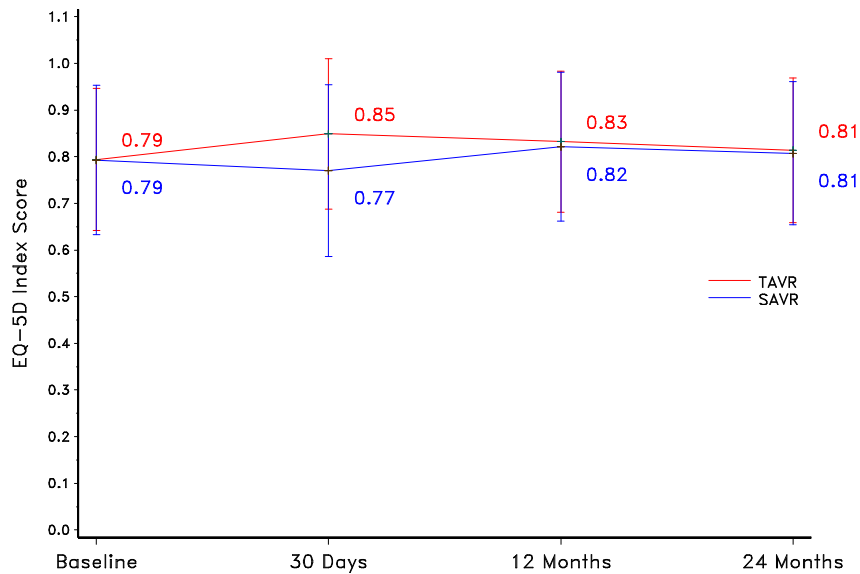


Note: Line plot with mean and standard deviation.



The EQ-5D index scores for the two treatment arms are shown in Figure 19.

**Figure 19: EQ-5D Index Score**



Note: Line plot with mean and standard deviation.

### 3. Adverse Events

The adverse events that occurred in the trial through 24 months are presented in Table 8.

**Table 8: Adverse Events (0-24 Months) - mITT Population**

Events	Summary Statistics*					
	0-30 Days		0-12 Months		0-24 Months	
	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR
All-cause mortality or disabling stroke	3.8% (30, 33)	2.8% (24, 29)	8.7% (66, 79)	8.1% (66, 74)	13.8% (87, 101)	12.3% (87, 97)
All-cause mortality	1.6% (13, 13)	2.1% (18, 18)	6.9% (51, 51)	6.8% (55, 55)	11.5% (70, 70)	11.2% (77, 77)
Cardiovascular	1.6% (13, 13)	2.0% (17, 17)	5.5% (41, 41)	4.8% (39, 39)	7.8% (51, 51)	7.5% (52, 52)
Valve-related †	0.0% (0, 0)	0.0% (0, 0)	0.1% (1, 1)	0.0% (0, 0)	0.1% (1, 1)	0.0% (0, 0)
Non-cardiovascular	0.0% (0, 0)	0.1% (1, 1)	1.4% (10, 10)	2.1% (16, 16)	4.0% (19, 19)	4.0% (25, 25)
Reintervention	0.1% (1, 1)	0.8% (7, 7)	0.4% (3, 3)	2.1% (17, 19)	0.4% (3, 3)	2.6% (20, 22)
All stroke	5.4% (43, 45)	3.3% (28, 29)	6.7% (52, 55)	5.3% (44, 45)	8.0% (58, 61)	6.3% (48, 50)

Events	Summary Statistics*					
	0-30 Days		0-12 Months		0-24 Months	
	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR
Disabling stroke	2.4% (19, 20)	1.2% (10, 11)	3.4% (26, 28)	2.2% (18, 19)	4.1% (29, 31)	2.4% (19, 20)
Non-disabling stroke	3.0% (24, 25)	2.1% (18, 18)	3.3% (26, 27)	3.1% (26, 26)	4.0% (29, 30)	4.1% (30, 30)
Life threatening/disabling bleeding	5.9% (47, 47)	5.7% (49, 51)	7.8% (60, 61)	7.1% (60, 66)	8.4% (63, 65)	8.0% (64, 72)
Major vascular complication	1.0% (8, 8)	5.9% (51, 55)	1.0% (8, 8)	6.3% (54, 59)	1.0% (8, 8)	6.3% (54, 59)
Acute kidney injury - Stage 3	1.3% (10, 10)	0.7% (6, 6)	1.3% (10, 10)	0.7% (6, 6)	1.3% (10, 10)	0.7% (6, 6)
MI	0.9% (7, 7)	0.8% (7, 7)	1.4% (11, 11)	1.9% (15, 15)	1.9% (13, 13)	2.6% (18, 18)
Aortic valve hospitalization	4.1% (32, 34)	2.8% (24, 26)	7.4% (55, 68)	8.4% (68, 104)	9.0% (62, 85)	13.2% (90, 134)
Permanent pacemaker implantation <sup>‡</sup>	6.8% (48, 48)	28.1% (217, 217)	9.0% (62, 64)	31.3% (239, 241)	10.3% (67, 70)	34.6% (253, 257)
Permanent pacemaker implantation <sup>§</sup>	6.5% (51, 51)	25.6% (220, 220)	8.6% (66, 68)	28.5% (242, 244)	9.8% (71, 74)	31.5% (256, 260)

\*Kaplan-Meier rate (# patients, # events).

<sup>†</sup>Valve-related death is any death caused by structural or non- structural valve dysfunction or aortic valve re-intervention.

<sup>‡</sup>Subjects with pacemaker or ICD at baseline are not included. Not adjudicated by CEC.

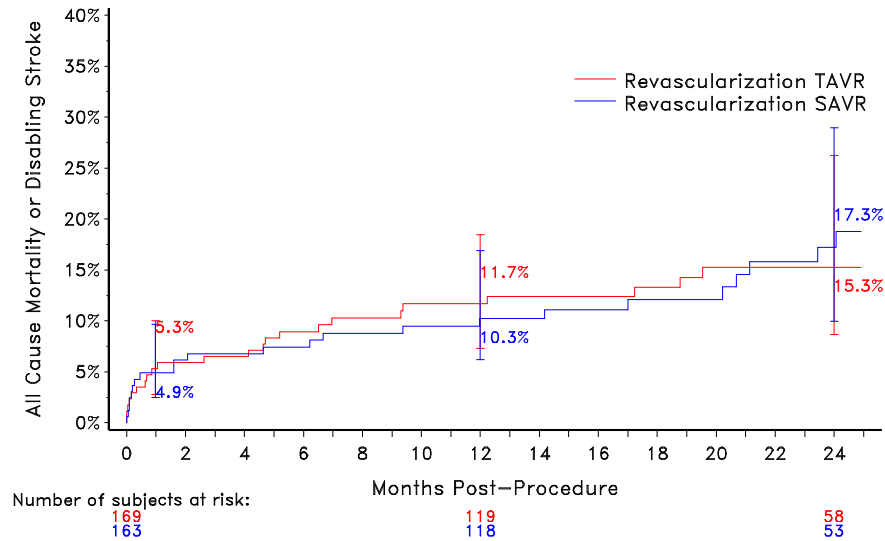
<sup>§</sup>Subjects with pacemaker or ICD at baseline are included. Not adjudicated by CEC.

#### 4. Subgroup analyses

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

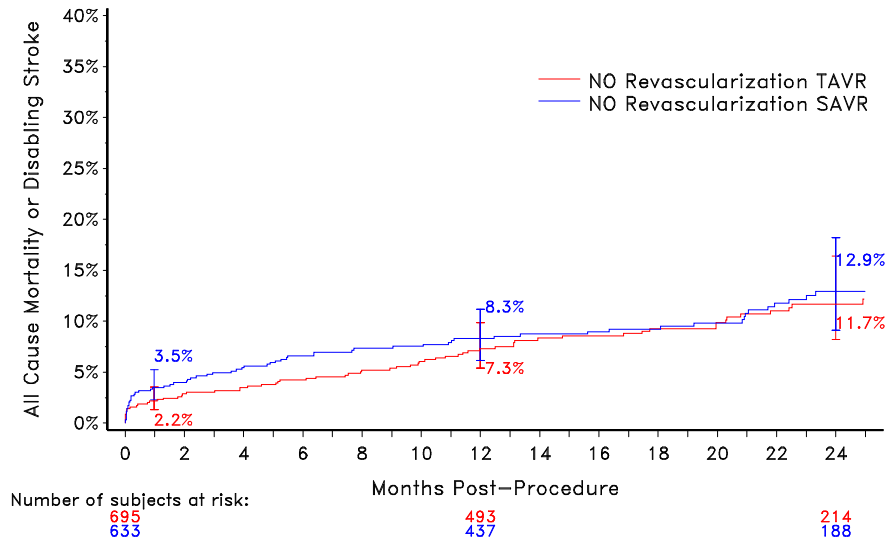
The K-M curves of all-cause mortality or disabling stroke are shown in Figures 20 and 21 for subjects with and without the need for concomitant revascularization, respectively.

**Figure 19: All-Cause Mortality or Disabling Stroke for Subjects with Need for Revascularization – mITT 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 Subjects without Need for Revascularization – mITT Population**

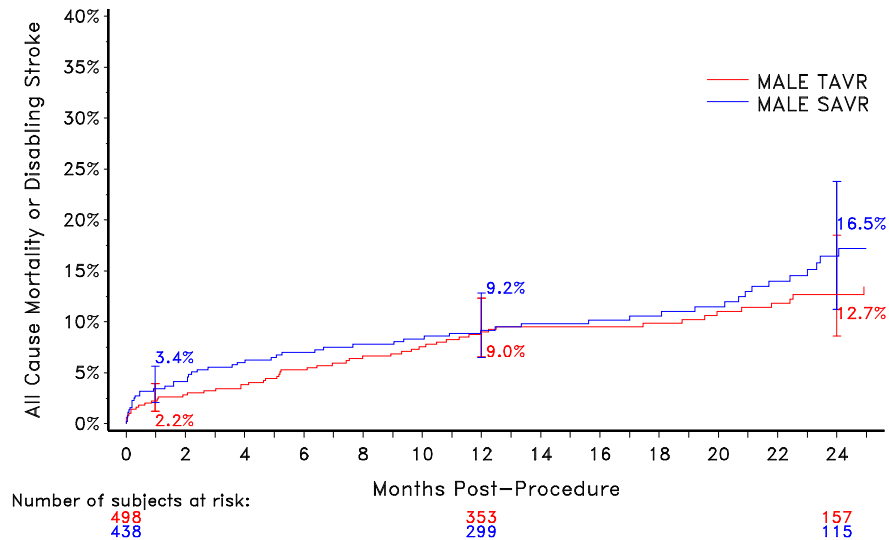


**Note:** The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion. The trial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

All-Cause Mortality or Disabling Stroke Stratified by Gender:

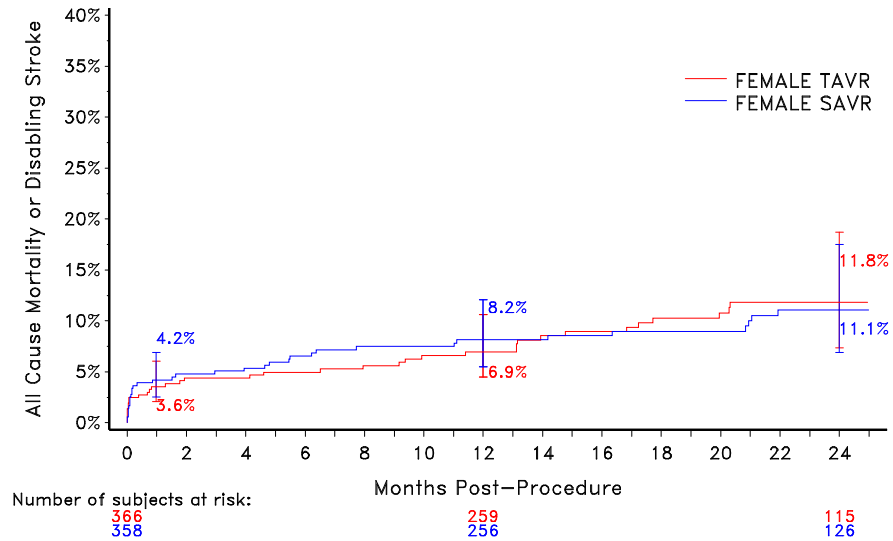
The K-M curves of all-cause mortality or disabling stroke are shown in Figures 21 and 22, for the male and female subjects, respectively.

**Figure 21: All-Cause Mortality or Disabling Stroke for Male Subjects - mITT 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 22: All-Cause Mortality or Disabling Stroke for Female Subjects - mITT Population**

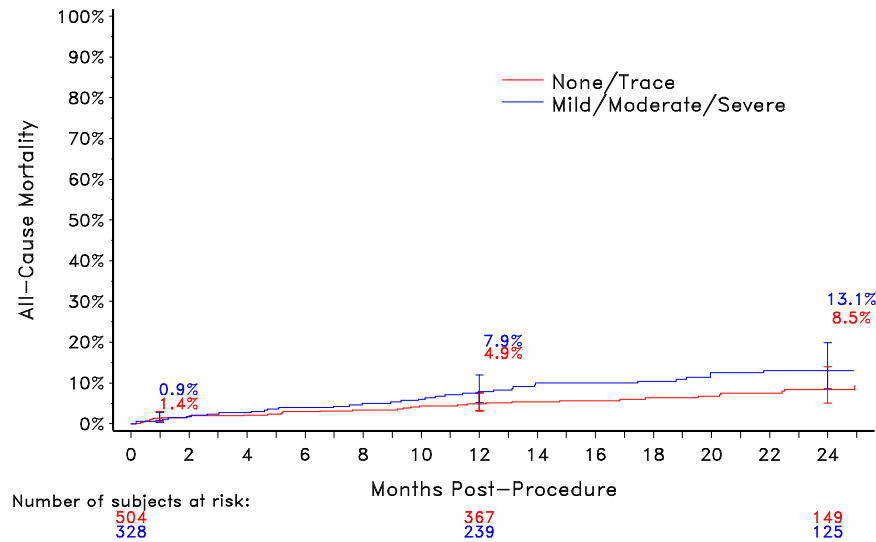


**Note:** The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion. The trial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

All-Cause Mortality by Severity of Aortic Regurgitation:

The K-M curves of all-cause mortality stratified by the severity of aortic regurgitation (none/trace or mild/moderate/severe) are shown in Figure 23.

**Figure 23: All-Cause Mortality by Severity of Aortic Regurgitation – TAVR Implanted Population**

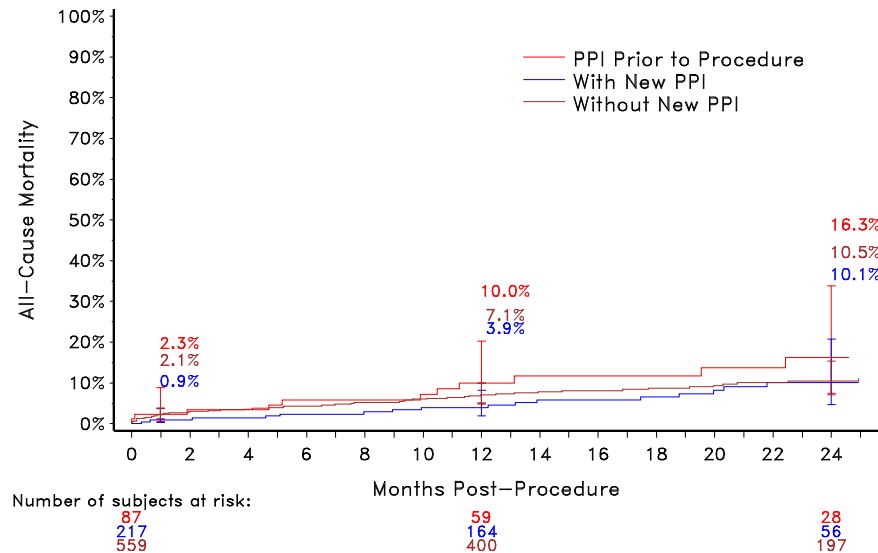


**Note:** The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion. The trial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

All-Cause Mortality by Need for Permanent Pacemaker Implantation (PPI) Post-TAVR:

The K-M curves of all-cause mortality stratified by the need for PPI are shown in Figure 24.

**Figure 24: All-Cause Mortality by Permanent Pacemaker Implantation – TAVR Implanted Population**



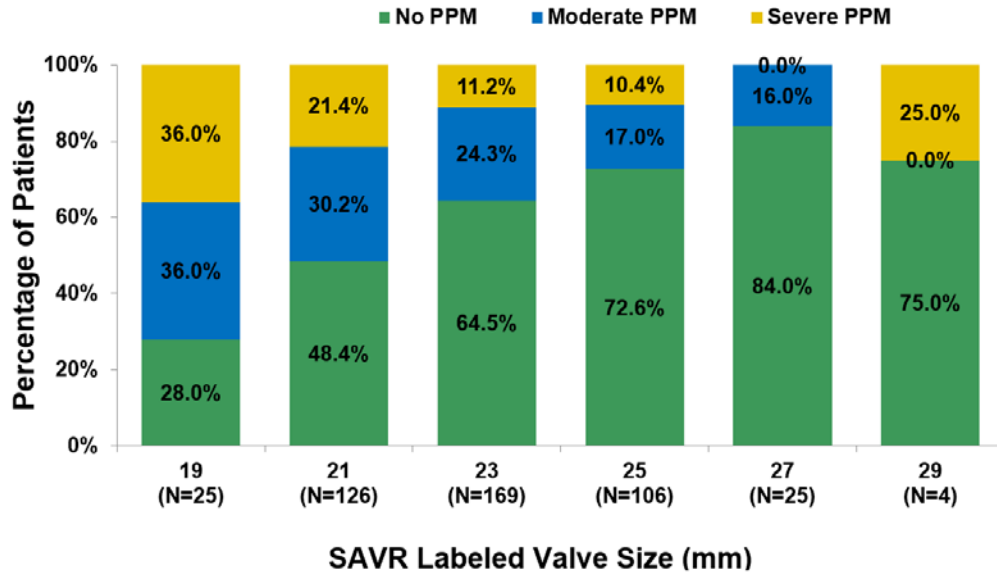
**Note:** The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion. The trial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

All-Cause Mortality by Patient Prosthesis Mismatch:

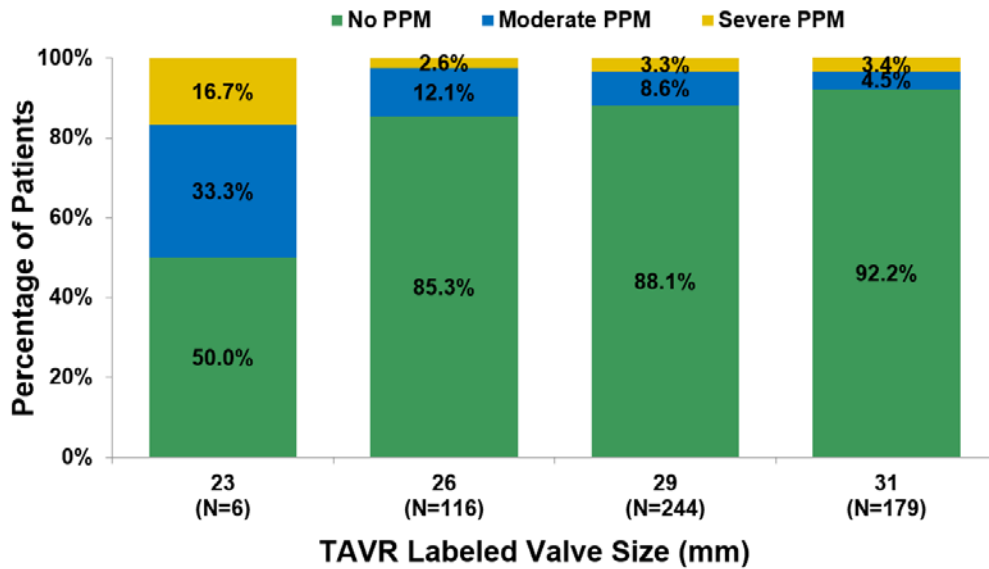
The site reported aortic annular perimeters were comparable between the two treatment arms (TAVR:  $78.3 \pm 7.2$  mm vs. SAVR:  $78.4 \pm 7.1$  mm). Patient prosthesis mismatch (PPM) is defined as an indexed EOA of 0.85-0.65  $\text{cm}^2/\text{m}^2$  (moderate) and  $< 0.65 \text{ cm}^2/\text{m}^2$  (severe) for subjects with a BMI  $< 30 \text{ kg}/\text{cm}^2$ , or 0.70-0.60  $\text{cm}^2/\text{m}^2$  (moderate) and  $< 0.60 \text{ cm}^2/\text{m}^2$  (severe) for subjects with a BMI  $\geq 30 \text{ kg}/\text{cm}^2$ . Figures 25 and 26 present the prevalence of PPM at 12 months in the two treatment arms by valve size. The majority of SAVR patients received a labeled valve size of  $\leq 23$  mm, and smaller valve sizes generally had more prevalent PPM. In comparison, PPM was less prevalent in the TAVR arm.

The K-M curves for all-cause mortality by PPM grade (none, moderate, and severe) are shown in Figures 27 and 28 for the SAVR and TAVR arm, respectively.

**Figure 25: Prevalence of PPM at 12 Months in the SAVR Arm by Valve Size**

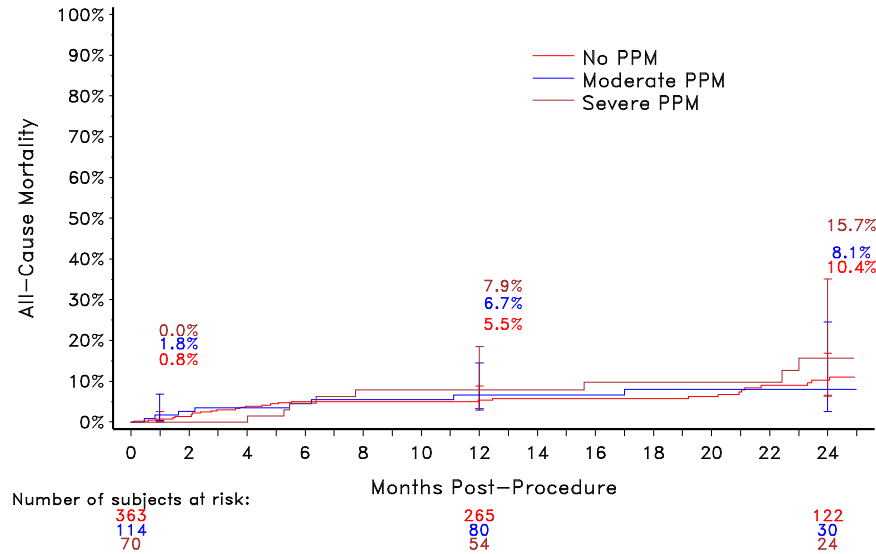


**Figure 26: Prevalence of PPM at 12 Months in the TAVR Arm by Valve Size**



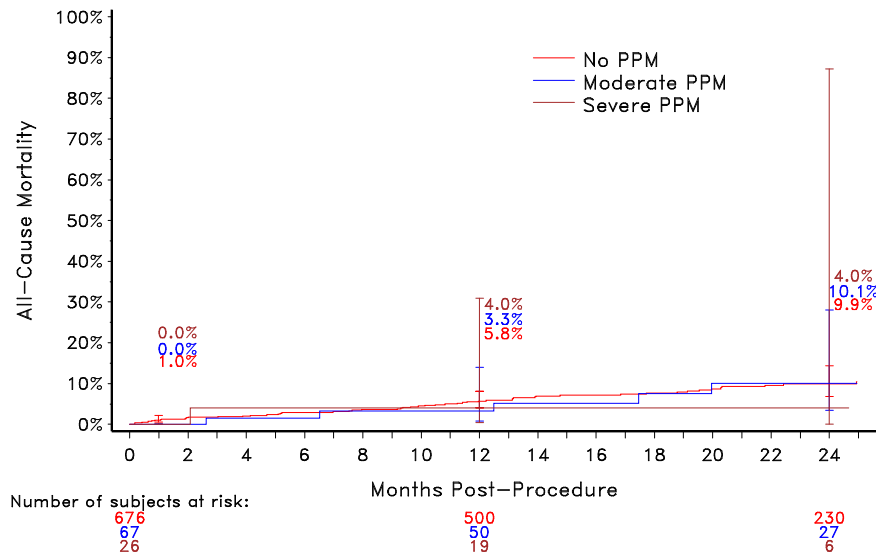


**Figure 27: All-Cause Mortality by PPM - SAVR Implanted Population**



**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 among the three subgroups.

**Figure 28: All-Cause Mortality by PPM - TAVR Implanted Set**



**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 among the three subgroups.

## 5. Other Study Observations

### Procedure Data:

The procedure data of the TAVR cohort of the trial is summarized in Table 9.

**Table 9: Procedural Data Summary for TAVR Subjects – mITT Population**

<b>Procedure Data</b>	<b>Summary Statistics<sup>*</sup> (N=864)</b>
Number of index procedures	863
Total delivery catheter in the body time (min)	15.0 ± 15.9
Type of anesthesia	
General	75.7% (653/863)
Conscious sedation	24.3% (210/863)
Respiratory support required	69.8% (602/863)
Access site	
Femoral	93.2% (804/863)
Percutaneous	81.3% (654/804)
Surgical cut-down	18.7% (150/804)
Iliac	0.5% (4/863)
Percutaneous	75.0% (3/4)
Surgical cut-down	25.0% (1/4)
Subclavian axillary	2.3% (20/863)
Direct aortic	4.1% (35/863)
Other	0.0% (0/863)
Total time in cath lab or OR (min)	190.8 ± 61.3
Total procedure time (min)	52.3 ± 32.7
Pre-TAVR balloon valvuloplasty performed	47.2% (407/863)
Post-TAVR balloon valvuloplasty performed	29.0% (250/863)

<sup>\*</sup> Continuous measures - Mean ± SD; categorical measures - % (no./Total no.). Data include subjects with the index procedure defined as the first procedure that the delivery catheter is introduced.

## 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 890 investigators, of which none were full-time or part-time employees of the sponsor and 59 had disclosable financial interests/arrangements related to the SURTAVI 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: 10
- Significant payment of other sorts: 54
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 1

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

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

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

## **XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES**

### **A. Effectiveness Conclusions**

In the clinical study, patients overall demonstrated clinically significant improvement in valve hemodynamics from baseline to 12 months. On average, the EOA increased from 0.78 cm<sup>2</sup> to 2.15 cm<sup>2</sup>, and the mean pressure gradient decreased from 47.17 mmHg to 8.29 mmHg in the TAVR patients. These trends were consistent with those observed in the SAVR patients. The post-procedural EOA was significantly larger and the mean gradient was significantly lower in TAVR subjects as compared to SAVR subjects. However, the incidence of post-procedural aortic regurgitation was greater in the TAVR patients as compared to SAVR patients.

The improvement in valve hemodynamics in the TAVR patients was further demonstrated through improvements from baseline in NYHA classification and KCCQ overall summary score. In the TAVR mITT population, 4.9% of the patients were in NYHA Class III or IV at 12 months as compared to 60.2% at baseline. This trend was comparable to that in the SAVR mITT population. The mean KCCQ overall summary score in the TAVR mITT population increased from 60.0 at baseline to 78.4 at 30 days. This improvement was significantly greater than that in the SAVR mITT population (59.9 at baseline to 66.1 at 30 days). Furthermore, the TAVR mITT population had

significantly shorter index procedure hospital stay than the SAVR mITT population ( $5.8 \pm 4.9$  days vs.  $9.8 \pm 8.0$  days).

## **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 pivotal clinical study has shown that TAVR with the CoreValve System or CoreValve Evolut R System was non-inferior to SAVR within a non-inferiority margin of 7% in the composite event rate of all-cause mortality or disabling stroke at 24 months (posterior median: 12.6% for TAVR vs. 14.0% for SAVR; posterior probability of non-inferiority  $> 0.9999$ ; mITT population). The K-M rates of all-cause mortality and disabling stroke at 12 months were clinically comparable between TAVR and SAVR patients (6.8% vs. 6.9% for all-cause mortality; 2.2% vs. 3.4% for disabling stroke).

## **C. Benefit-Risk Conclusions**

The probable benefits of the Medtronic CoreValve System and the CoreValve Evolut R System include improved valve hemodynamic performance, improved functional status as measured by the NYHA classification and improved health status/QoL at 12 months post-procedure.

The probable risks of the Medtronic CoreValve System and the CoreValve Evolut R System include procedure related complications such as death, stroke, myocardial infarction, major vascular complications, bleeding, conduction disturbance, and acute kidney injury.

### **1. Patient Perspectives**

This submission did not include specific information on patient perspectives for the Medtronic CoreValve System and the CoreValve Evolut R System. However, since TAVR with the Medtronic CoreValve System and the CoreValve Evolut R System provides a less invasive alternative to SAVR, FDA believes that many patients would prefer the TAVR therapy.

In conclusion, given the available information above, the data support that for patients with severe native aortic stenosis who are at intermediate or greater risk for open aortic valve replacement surgery, the probable benefits outweigh the probable risks.

## **D. Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness

of the Medtronic CoreValve System and the CoreValve Evolut R System for the replacement of native aortic valves in symptomatic severe aortic stenosis patients who are deemed to be at intermediate or greater surgical risk, defined as having a predicted risk of surgical mortality of  $\geq 3\%$  at 30 days, based on the STS risk score and other clinical comorbidities unmeasured by the STS risk calculator. FDA has determined this conclusion is also applicable to the Medtronic CoreValve Evolut PRO System.

### **XIII. CDRH DECISION**

CDRH issued an approval order on July 10, 2017. The final conditions of approval cited in the approval order are described below:

- 1. Post-Approval Study - Continued Follow-up of the Medtronic CoreValve System and CoreValve Evolut R System “Intermediate Risk” Indication Premarket Cohort:** The study will consist of all living subjects who were enrolled under the IDE. The objective of this study is to characterize the clinical outcomes annually through 10 years post-procedure. The safety and effectiveness endpoints include all-cause mortality, all stroke (disabling and non-disabling), life-threatening bleeding, 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 System, CoreValve Evolut R System, and CoreValve Evolut PRO System “Intermediate Risk” Indication 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 Medtronic CoreValve System, CoreValve Evolut R System, and CoreValve Evolut PRO System used for the “intermediate risk” indication over the next 2 years. The applicant has also agreed to link the data to Centers for Medicare and Medicaid Services (CMS) database for long-term surveillance of these patients through 5 years post implantation. 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 2-5 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.